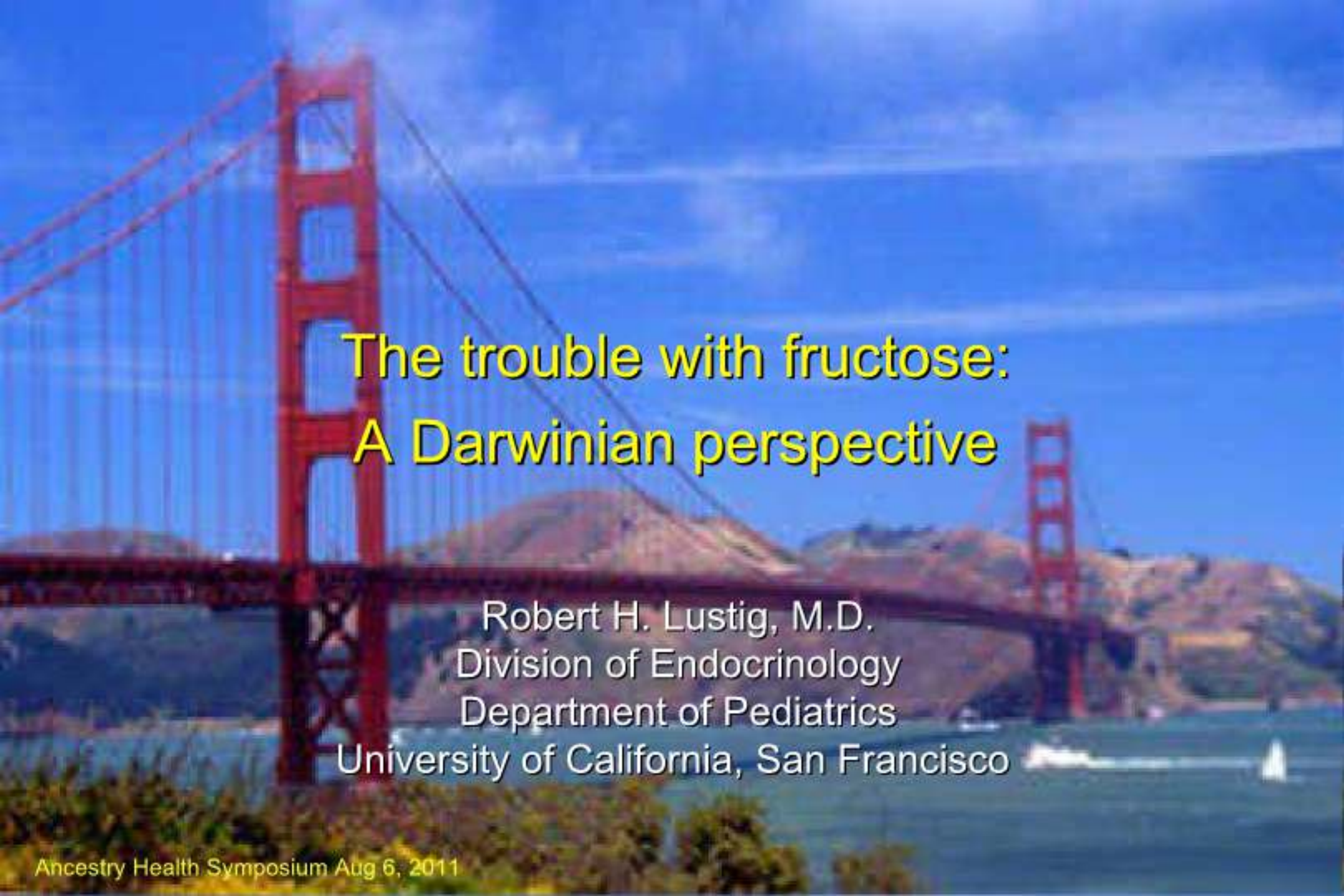

The trouble with fructose: A Darwinian perspective

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Division of Endocrinology
Department of Pediatrics
University of California, San Francisco

Ancestry Health Symposium Aug 6, 2011

- No disclosures

Introduction

- Obesity continues to worsen, both in prevalence and severity
- Obesity is increasing in all developed (and developing) countries
- Obesity is increasing in all age groups, and especially in children
- Recidivism is high

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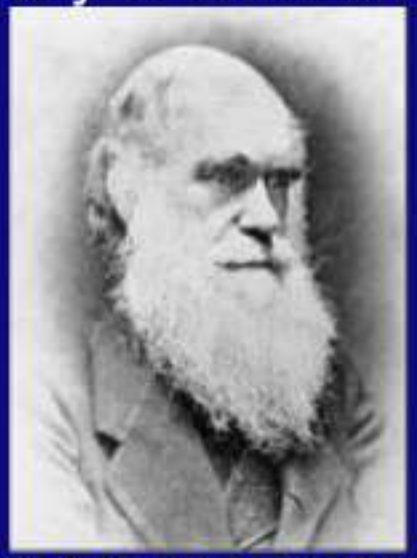

The obvious explanation:

Gluttony and sloth

The evolutionary explanation:

A mismatch between our environment and our biochemistry

What's the selective advantage to obesity?

- Energy storage for a rainy day (month, year, decade)

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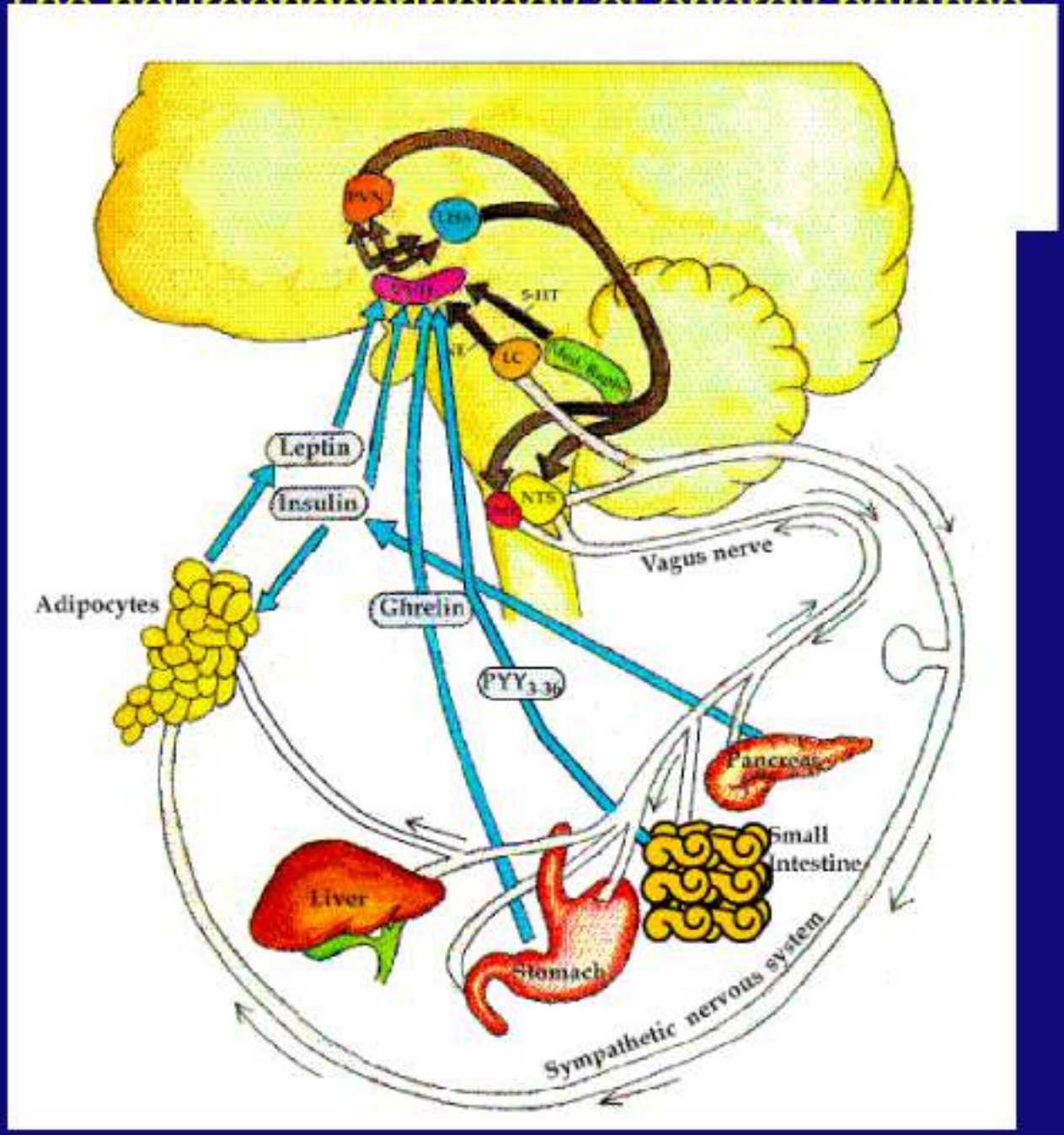
How is this selective advantage achieved?

- Leptin resistance
- Insulin resistance

The neuroendocrinology of energy balance



PARADOX:

If you give a 5 year old kid a cookie:

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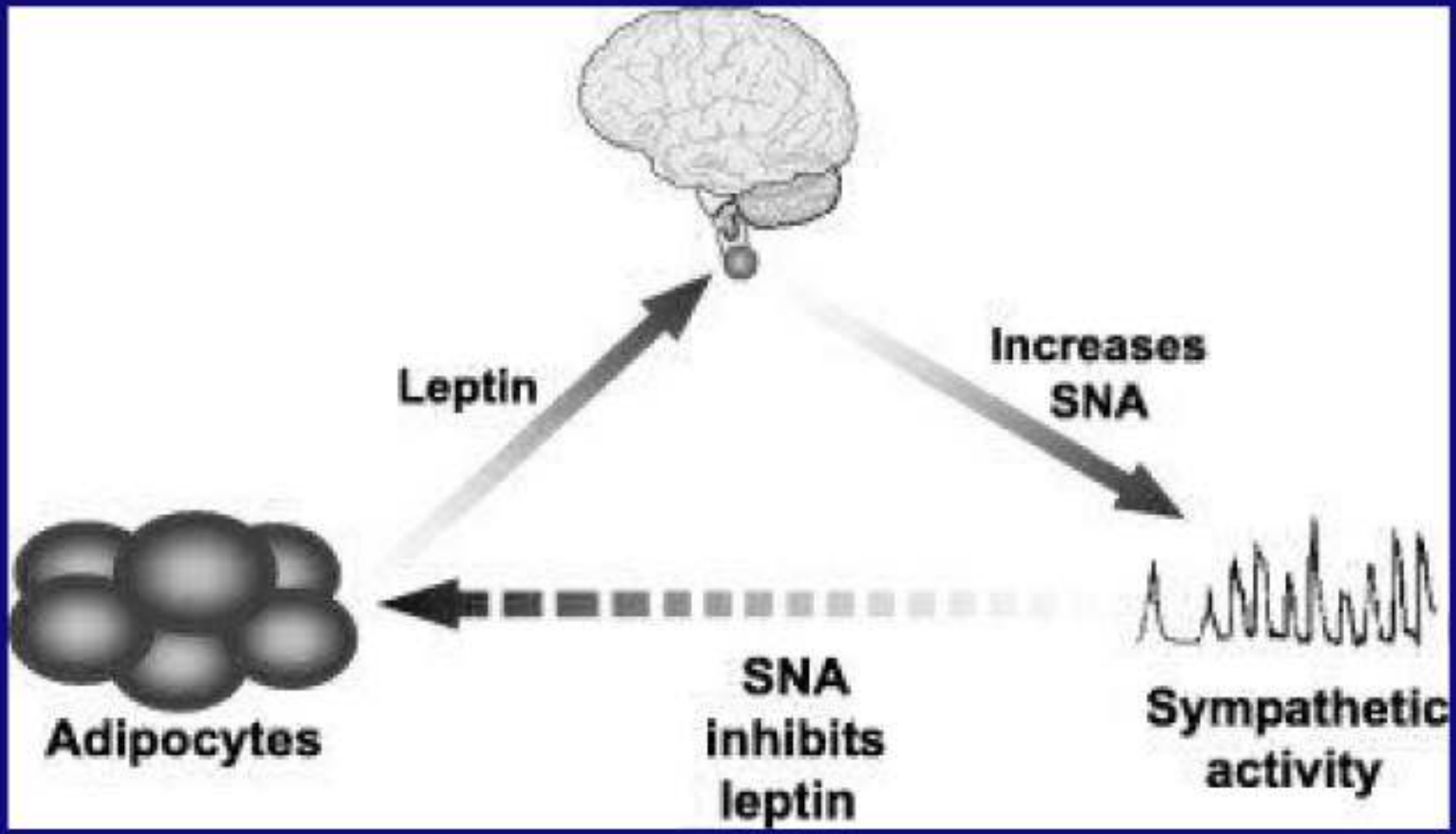
If you give a 5 year old kid a cookie:

Leptin stimulates the SNS



Mark et al. Acta Physiol Scand 177:345, 2003

PARADOX:

But if you give a 5 year old
obese kid a cookie:

PARADOX:

But if you give a 5 year old obese kid a cookie:

The physiology of leptin:

The Starvation Response

Dexfenfluramine

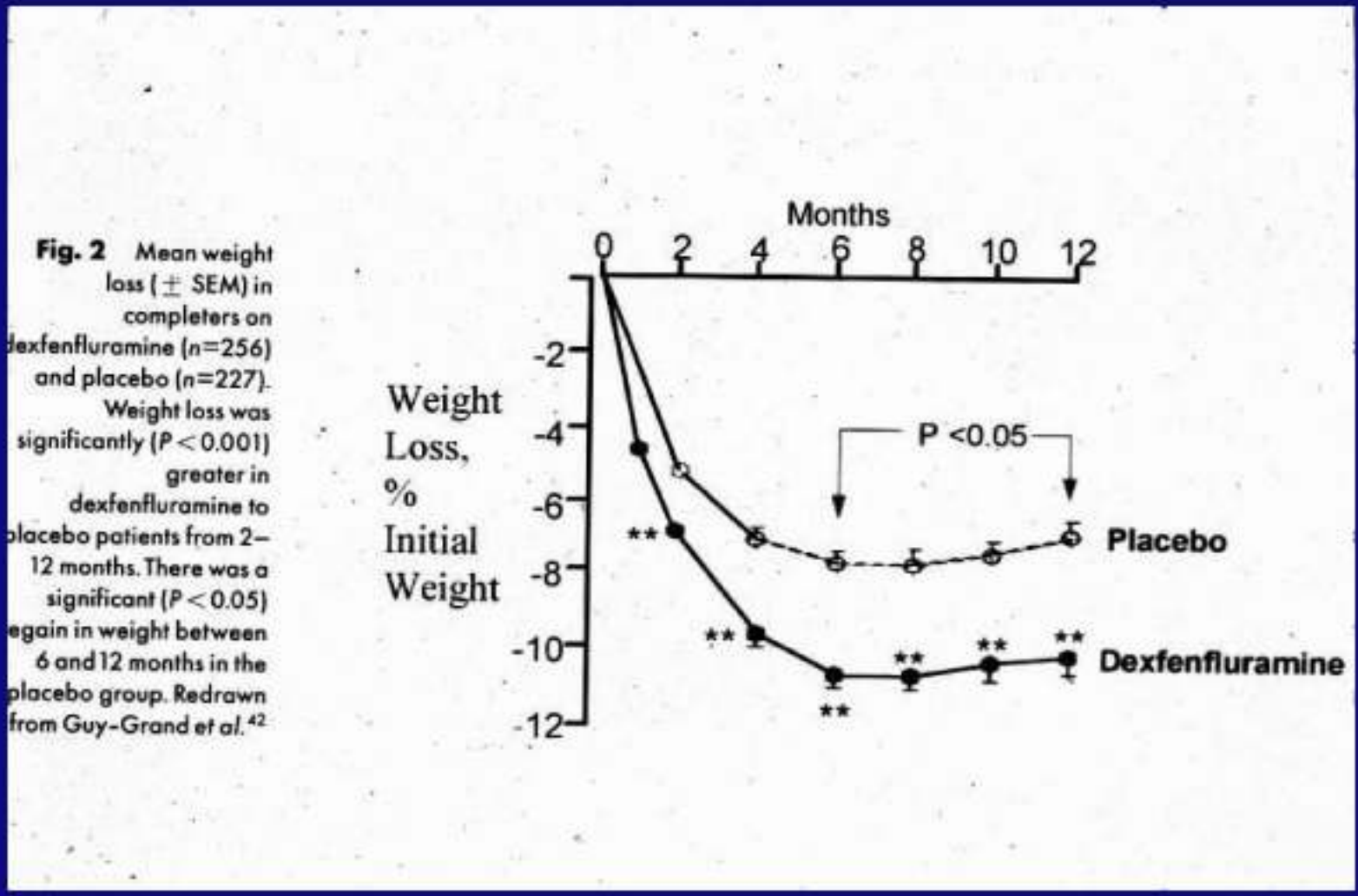
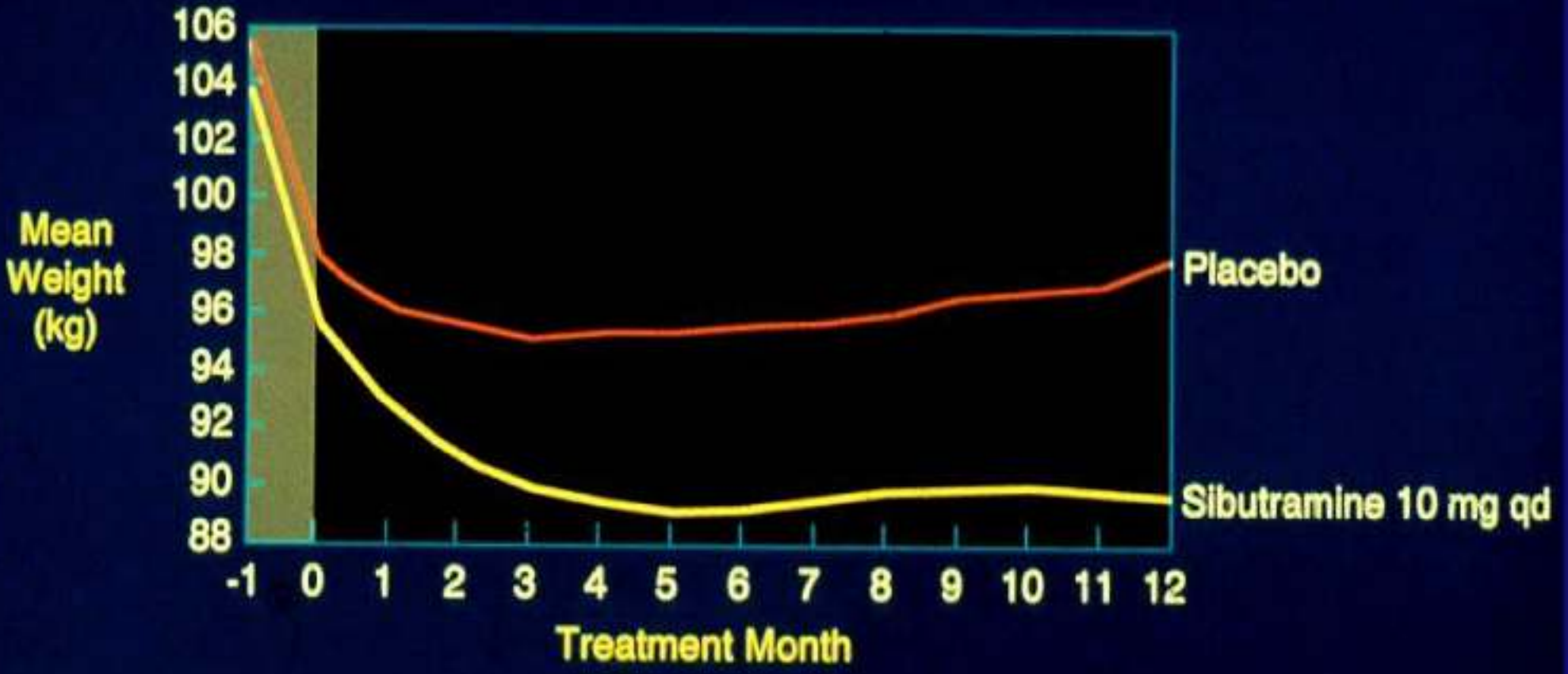


Fig. 2 Mean weight loss (± SEM) in completers on dexfenfluramine (n=256) and placebo (n=227). Weight loss was significantly ($P < 0.001$) greater in dexfenfluramine to placebo patients from 2–12 months. There was a significant ($P < 0.05$) regain in weight between 6 and 12 months in the placebo group. Redrawn from Guy-Grand *et al.*[42]

SB 1049: Mean Weight During 1-Year Trial



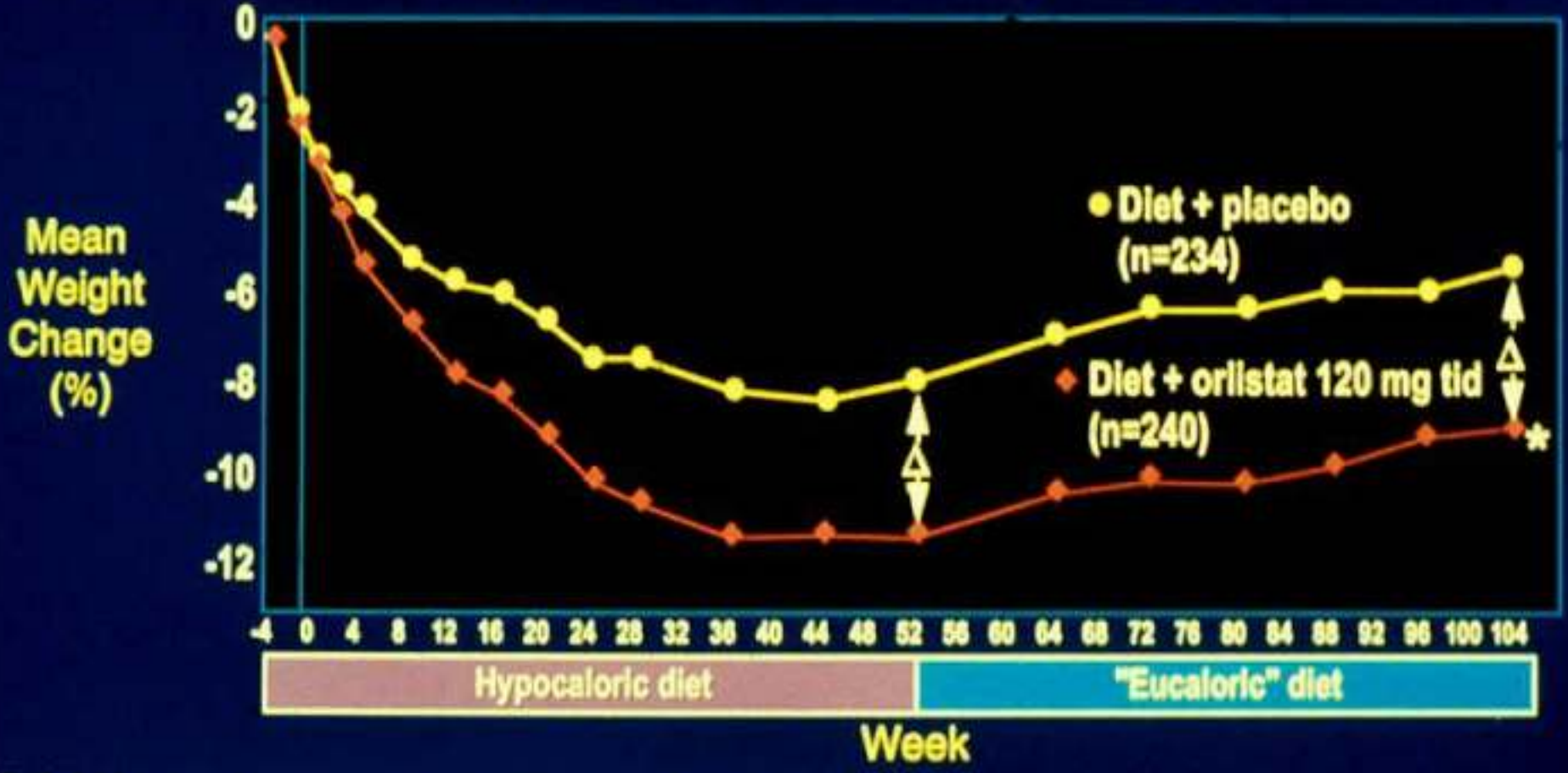
$P<0.001$ for months 1 to 12, sibutramine vs placebo.

▭ = very low calorie diet.

Apfelbaum et al. *Am J Med.* 1998. In press.

Efficacy: Orlistat

Mean Percent Change From Initial Body Weight Over 2 Years



*$P<0.0001$; least squares mean difference from placebo.

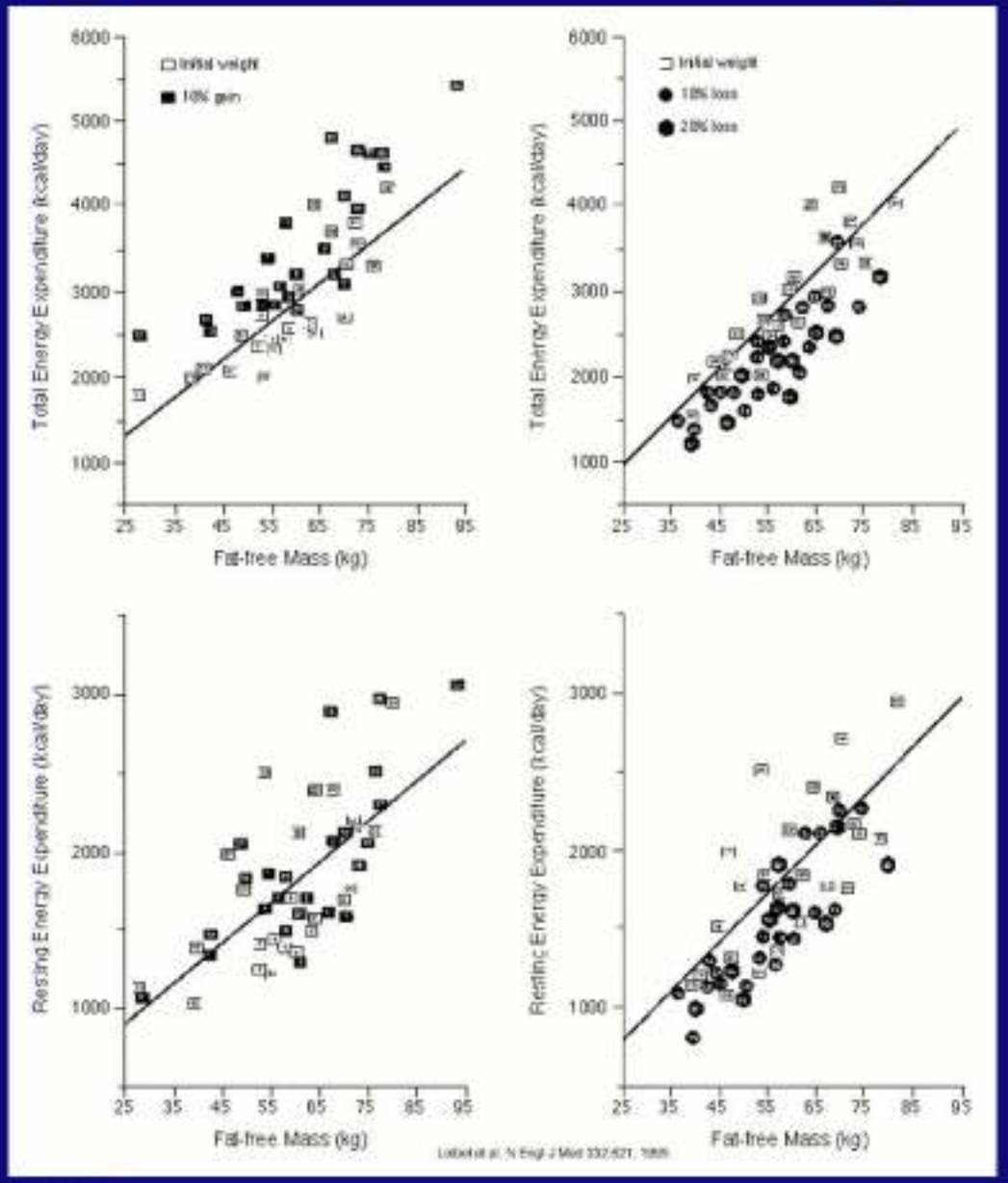
Orlistat NDA, data on file, Roche Laboratories, Inc.

Why the negative plateau with weight loss?

Because of decreased energy expenditure, to offset the decreased caloric intake

- Decreased non-exercise associated thermogenesis (NEAT)
- Decreased resting energy expenditure
  - Decreased thermic effect of food
  - mitochondrial adaptation (UCP's?)

Weight loss lowers REE/FFM by 20%



Leibel et al. N Engl J Med 332:621, 1995

Energy Expenditure = "Quality of Life"

Decreased energy expenditure:

- hypothyroidism
- starvation

Increased energy expenditure:

- exercise
- caffeine
- ephedrine (banned)

Autonomic Function during the Starvation Response

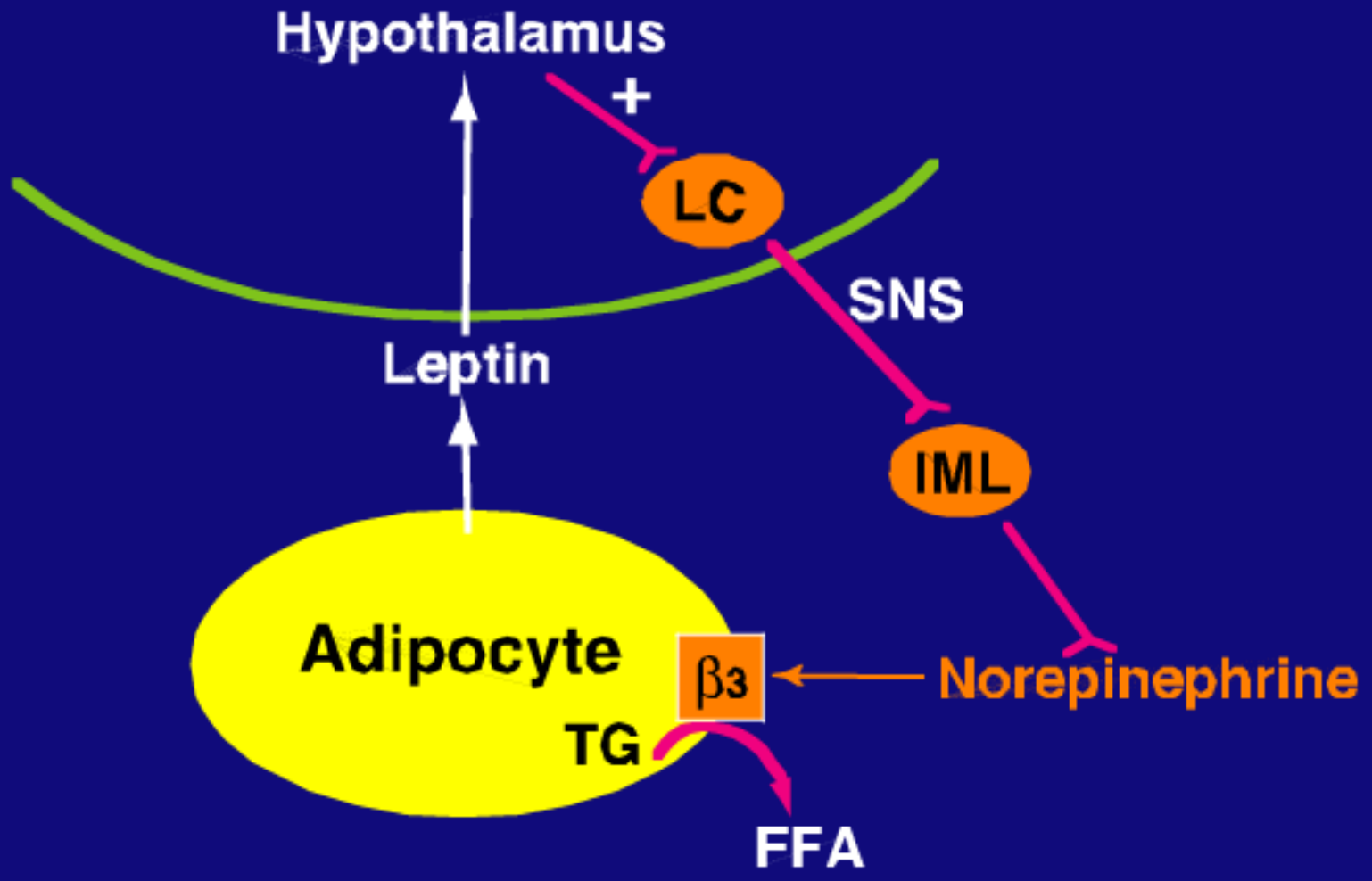
In response to declining leptin:

- Reduced sympathetic activity
- decreased lipolysis
- decreased gluconeogenesis
- decreased energy expenditure

- Increased vagal activity
- reduced myocardial oxygen consumption
- increased adipocyte insulin sensitivity
- increased insulin secretion
- increased energy storage

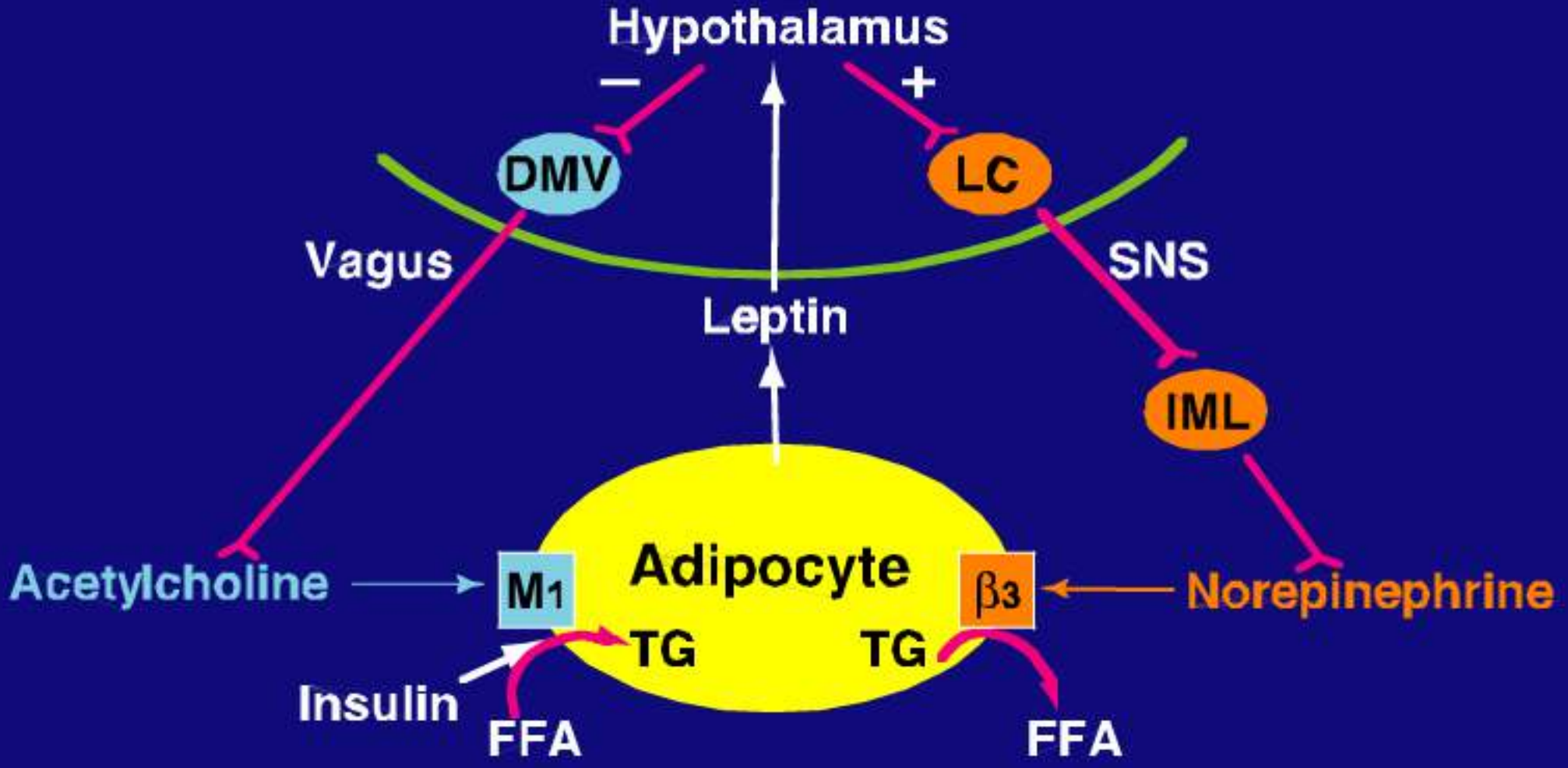
Aronne et al. Am J Phys 269:R222, 1995

Autonomic Innervation of the Adipocyte



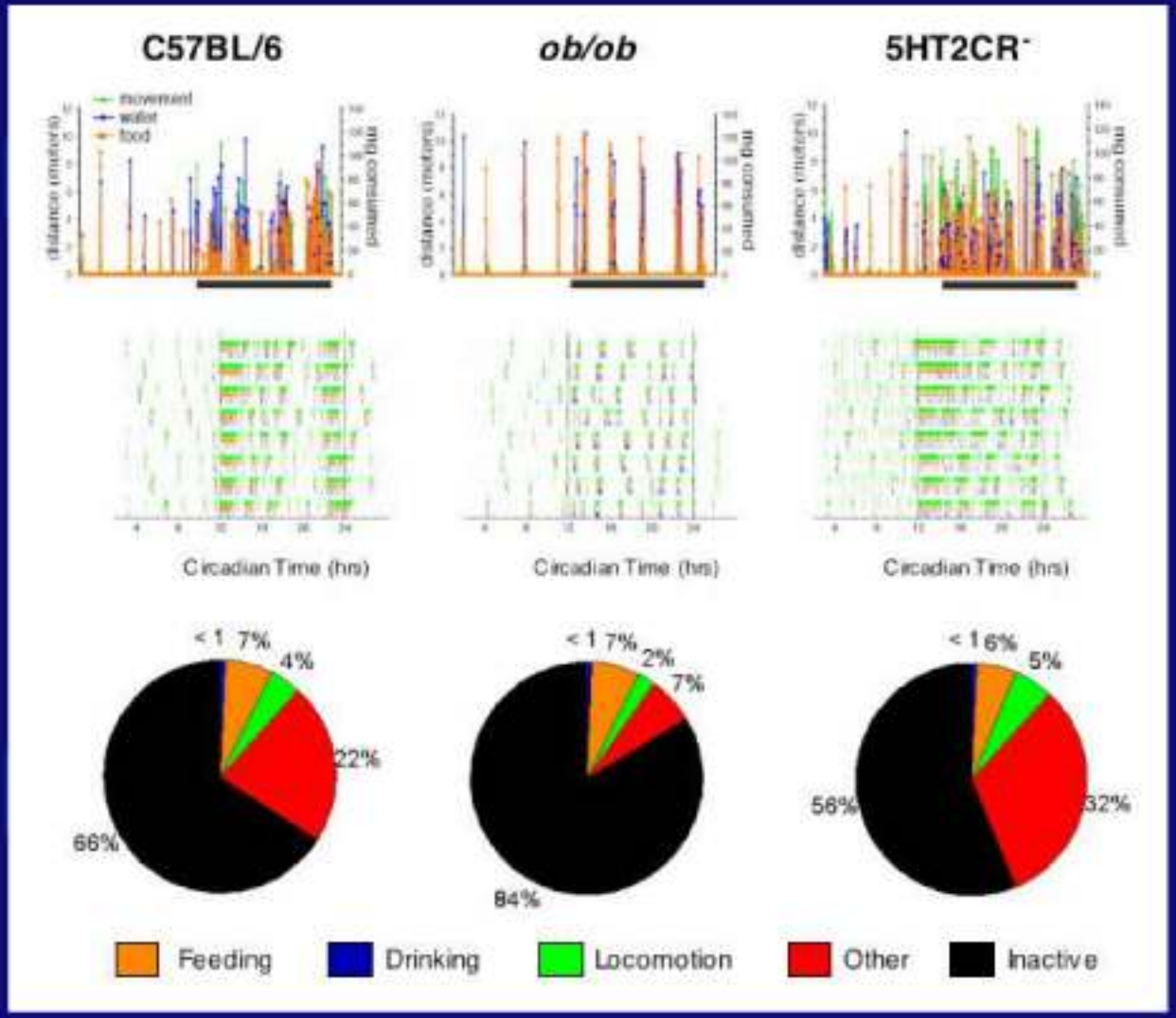
Lustig, In: Donohoue (ed) Obesity Research and Clinical Applications, Humana, 2008

Autonomic Innervation of the Adipocyte



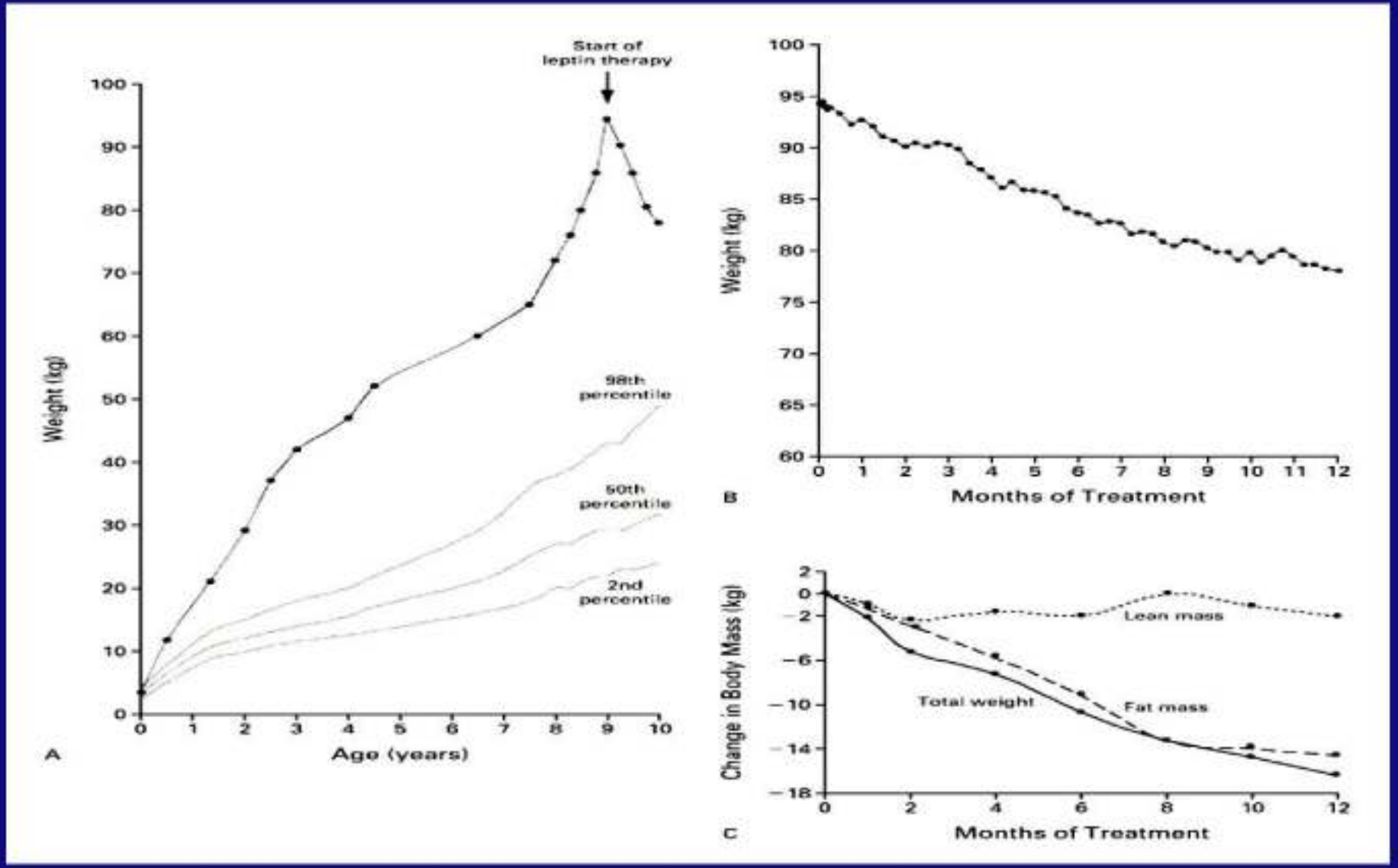
Lustig, In: Donohoue (ed) Obesity Research and Clinical Applications, Humana, 2008

Lifestyles of the obese (mouse)



Nonogaki et al. Diabetes 52:315, 2003

Leptin promotes weight loss in a leptin-deficient patient



Farooqi et al. N Engl J Med 341:913, 1999

Leptin Therapy of Leptin Deficiency

Age 3.5 years

Age 8 years

Farooqi, et al. JCI Oct. 2002

Obese subjects are leptin resistant

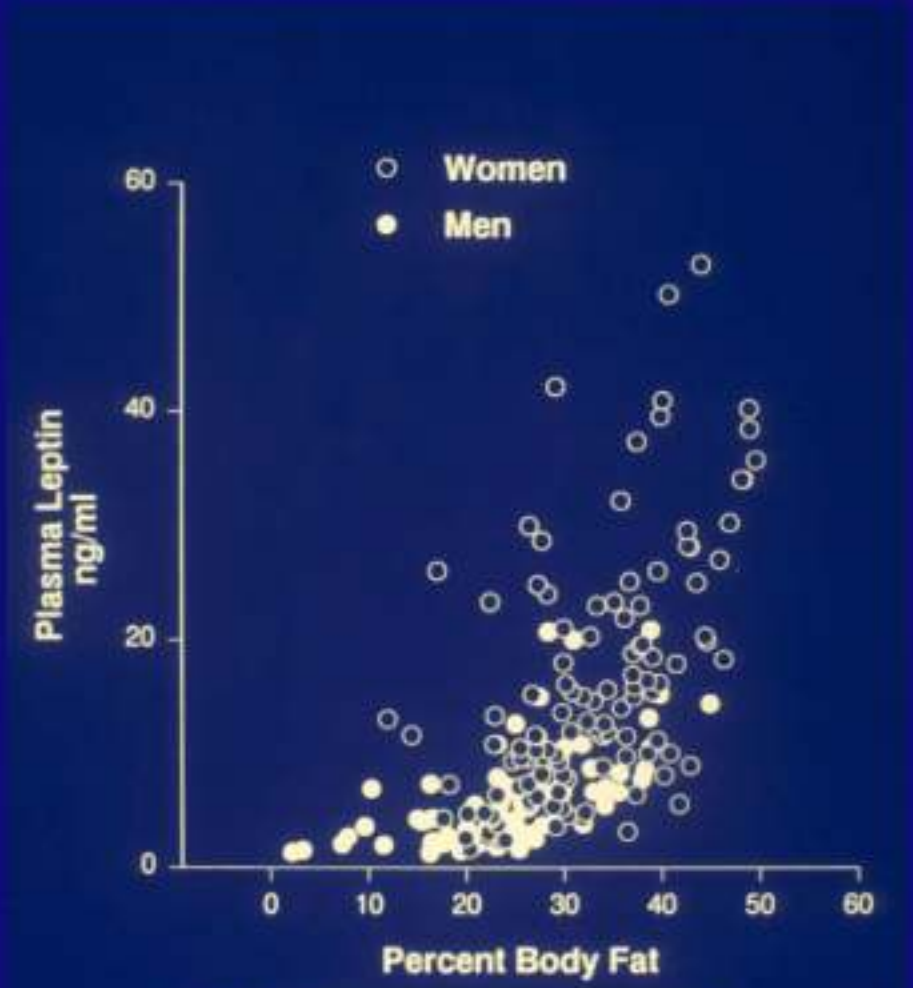
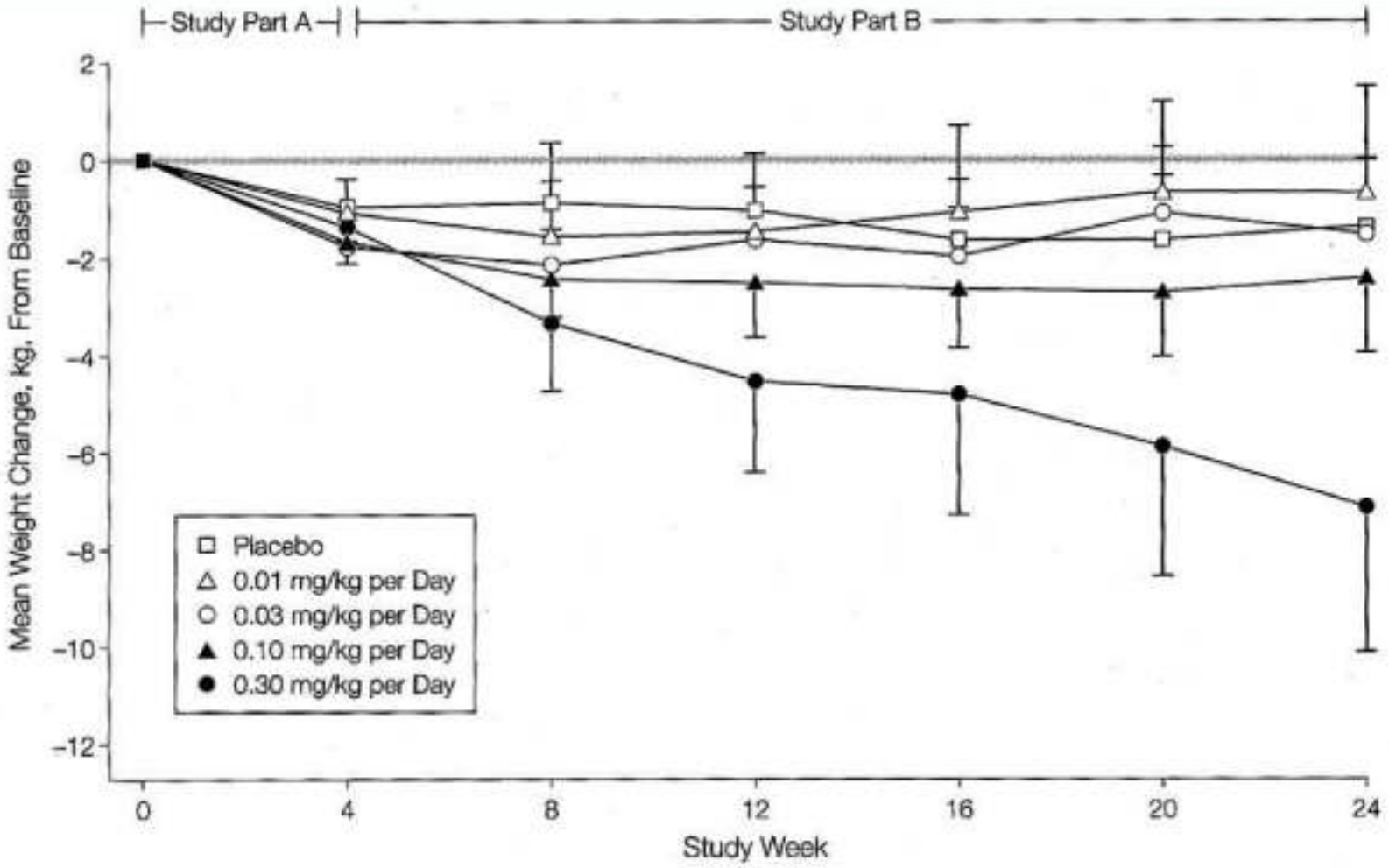


FIG. 2. Plasma leptin in 204 subjects.

Ostlund *et al.* JCEM 81:3909, 1996

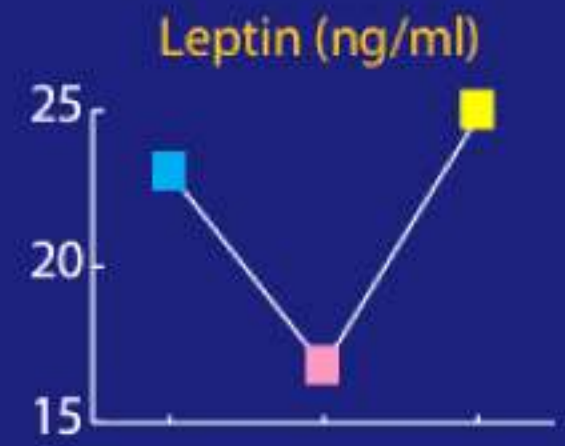
Leptin resistance prevents leptin-induced weight loss in obese adults

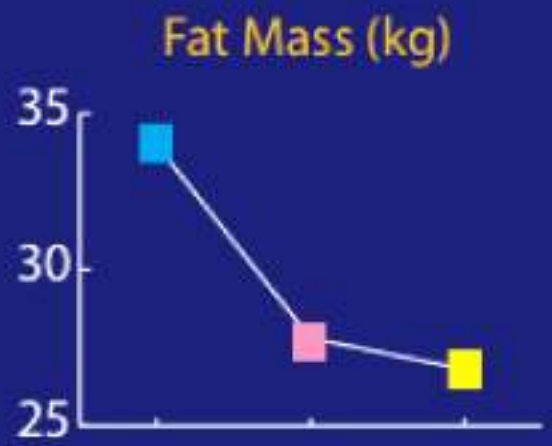


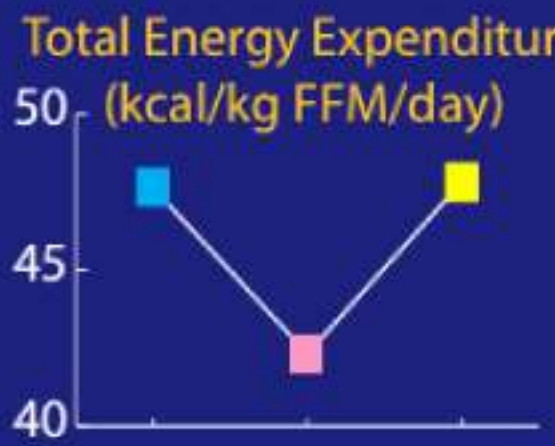
Error bars indicate SEM; gray line indicates baseline. The number of subjects is not constant over the course of the study (see Table 2).

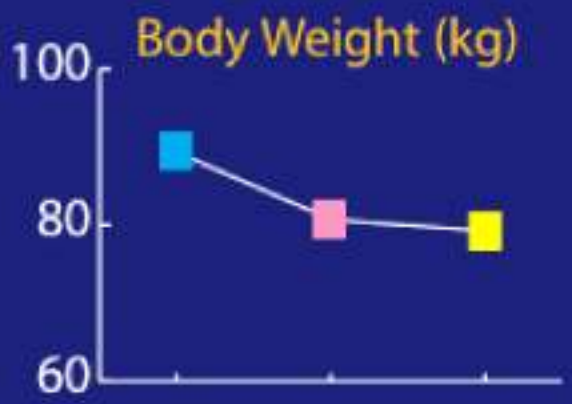
Heymsfield et al. JAMA 282:1568, 1999

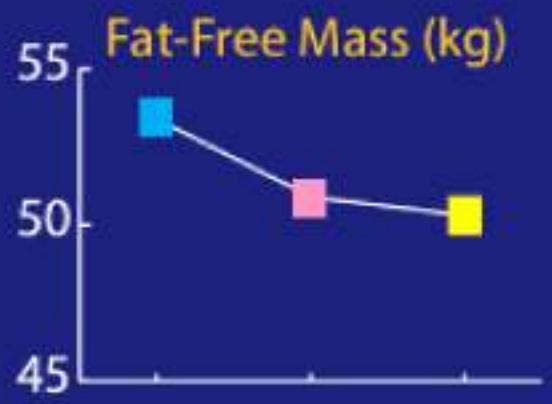
Leptin reverses metabolic effects of caloric deprivation

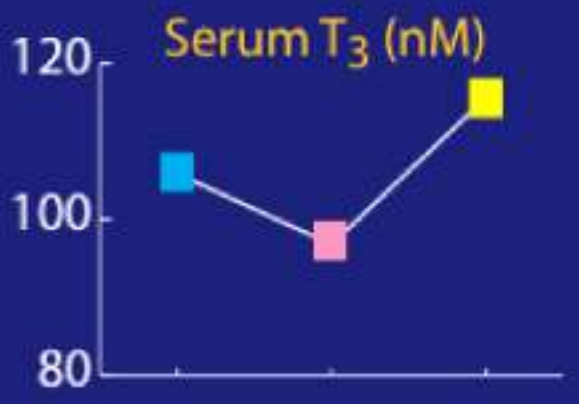












Rosenbaum et al. JCEM 87:2391, 2002

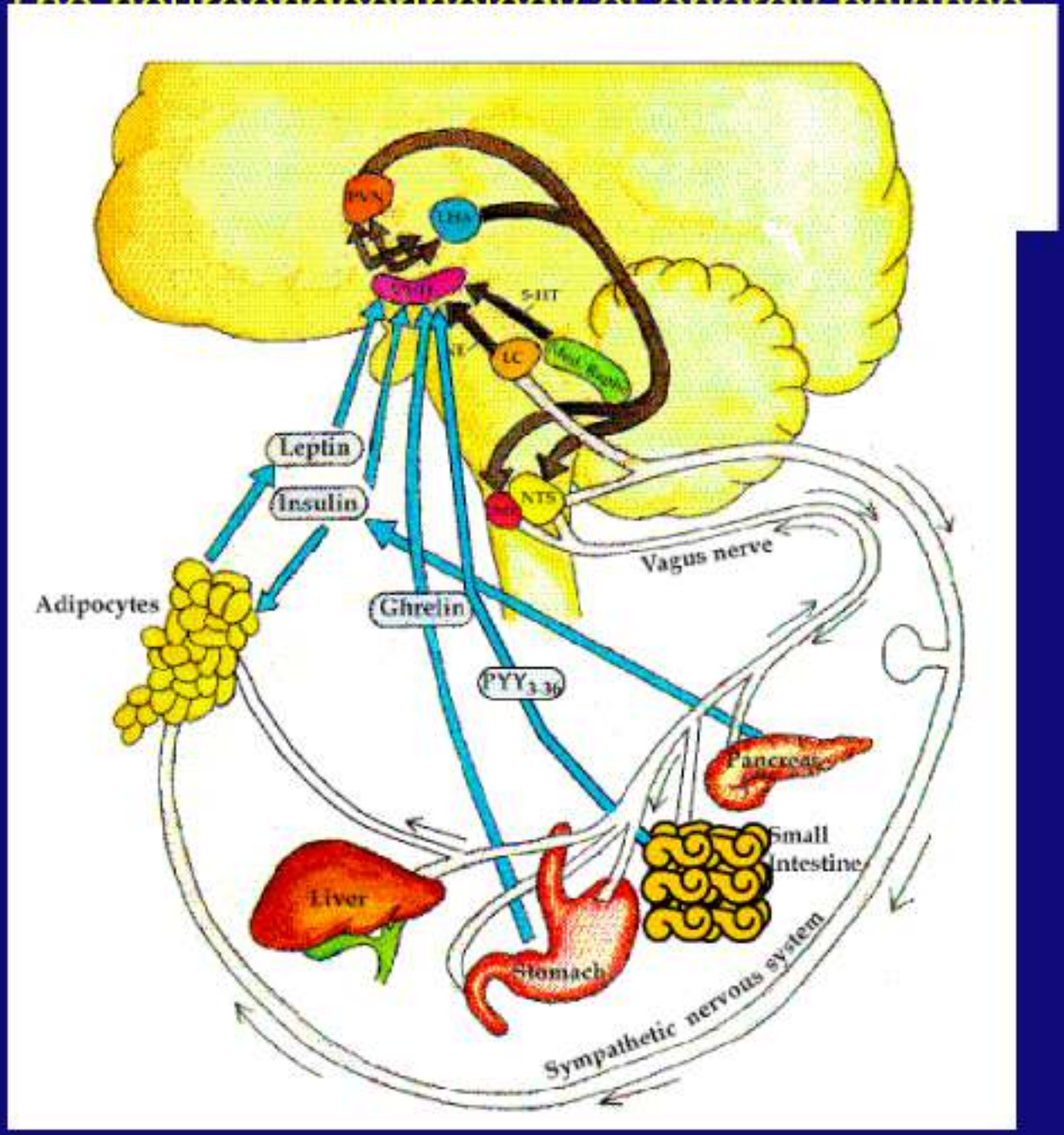
Leptin and Leptin Resistance

- Leptin levels are a function of adipocyte energy stores
- Leptin tells your brain how thin you are, not how fat you are
- The brain perceives leptin deficiency as a state of starvation
- Leptin deficiency causes energy expenditure to decrease, and thyroid levels to decline, while leptin repletion corrects them
- Caloric restriction leads leptin decline before weight loss, and promotes drive to resume caloric intake
- Obese subjects are hyperleptinemic and "leptin resistant"
- If we could fix leptin resistance, there wouldn't be obesity

What causes leptin resistance?

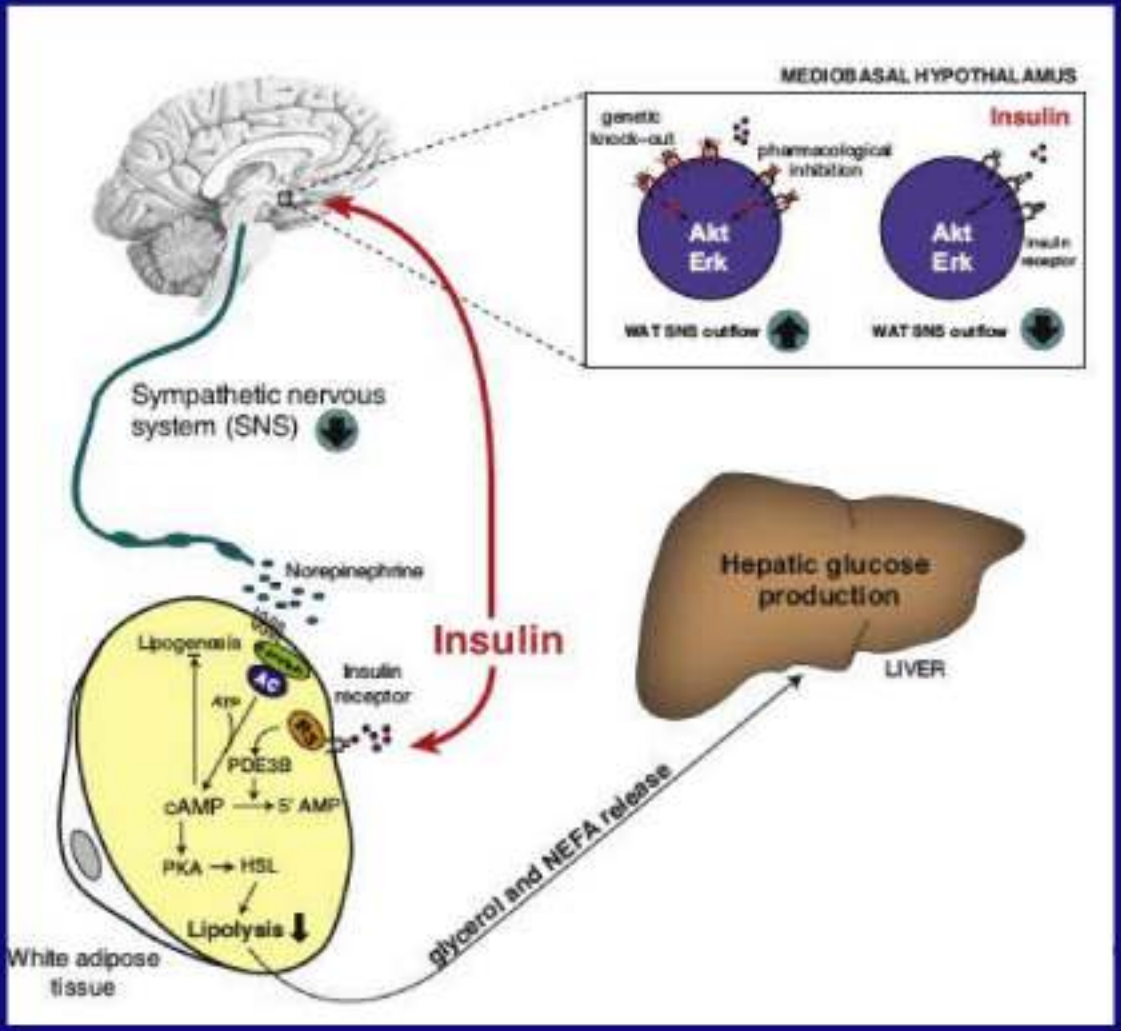
- Genetic
- Anatomic
- Functional

The neuroendocrinology of energy balance



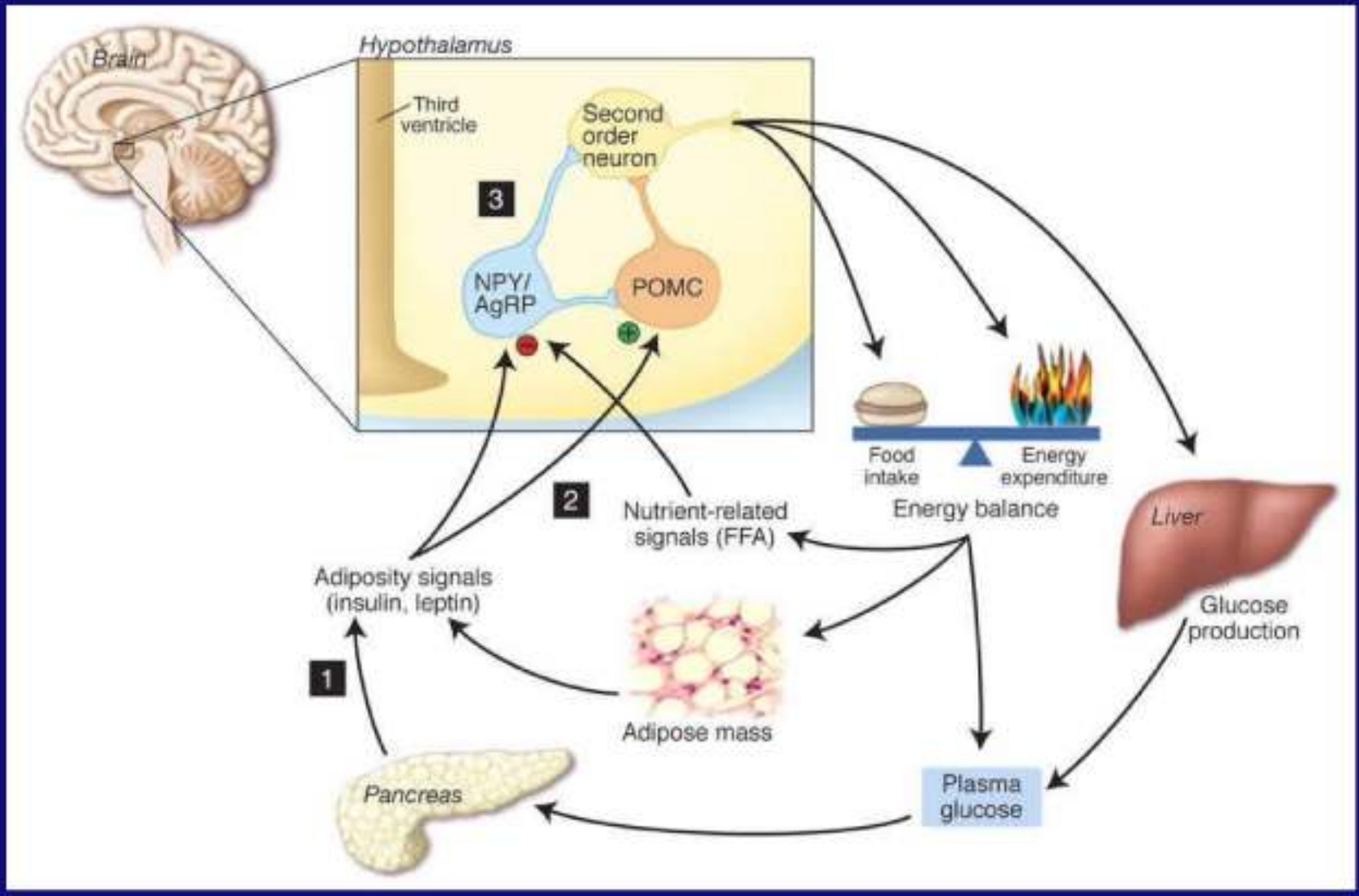
Effects of Insulin on the Adipocyte

- Stimulates Glut4 mRNA and protein
- Stimulates Acetyl-CoA Carboxylase
- Stimulates Fatty Acid Synthase
- Stimulates Lipoprotein Lipase
- Hypothalamic actions inhibits lipolysis by suppressing SNS tone and Hormone-Sensitive Lipase



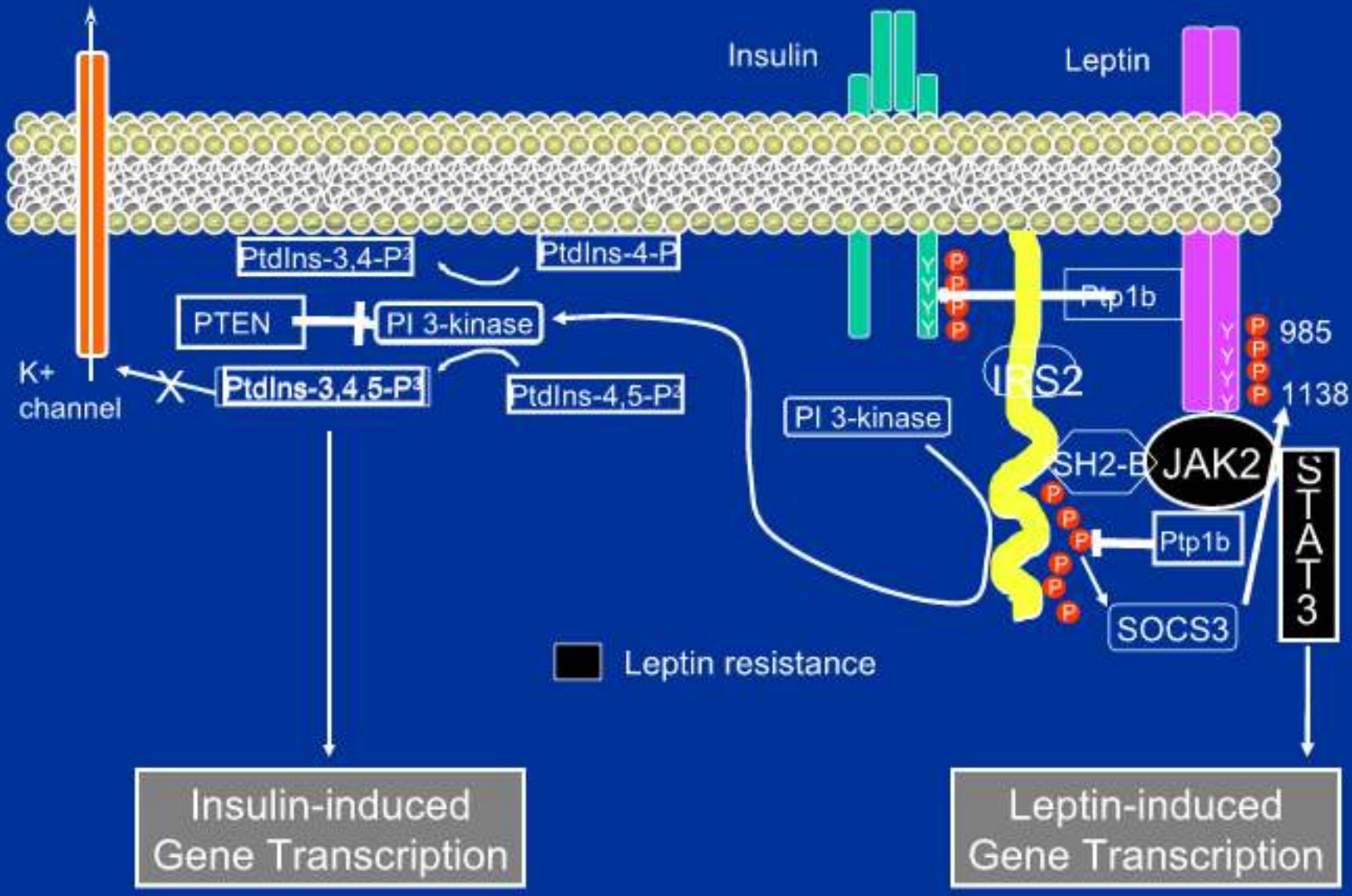
Scherer et al. Cell Metab doi10.1016/j.cmet.2011.01.008

Leptin and insulin act on the same VMH neurons



Schwartz et al. Science 307:375, 2005

Knockout studies of leptin resistance: leptin pathway



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

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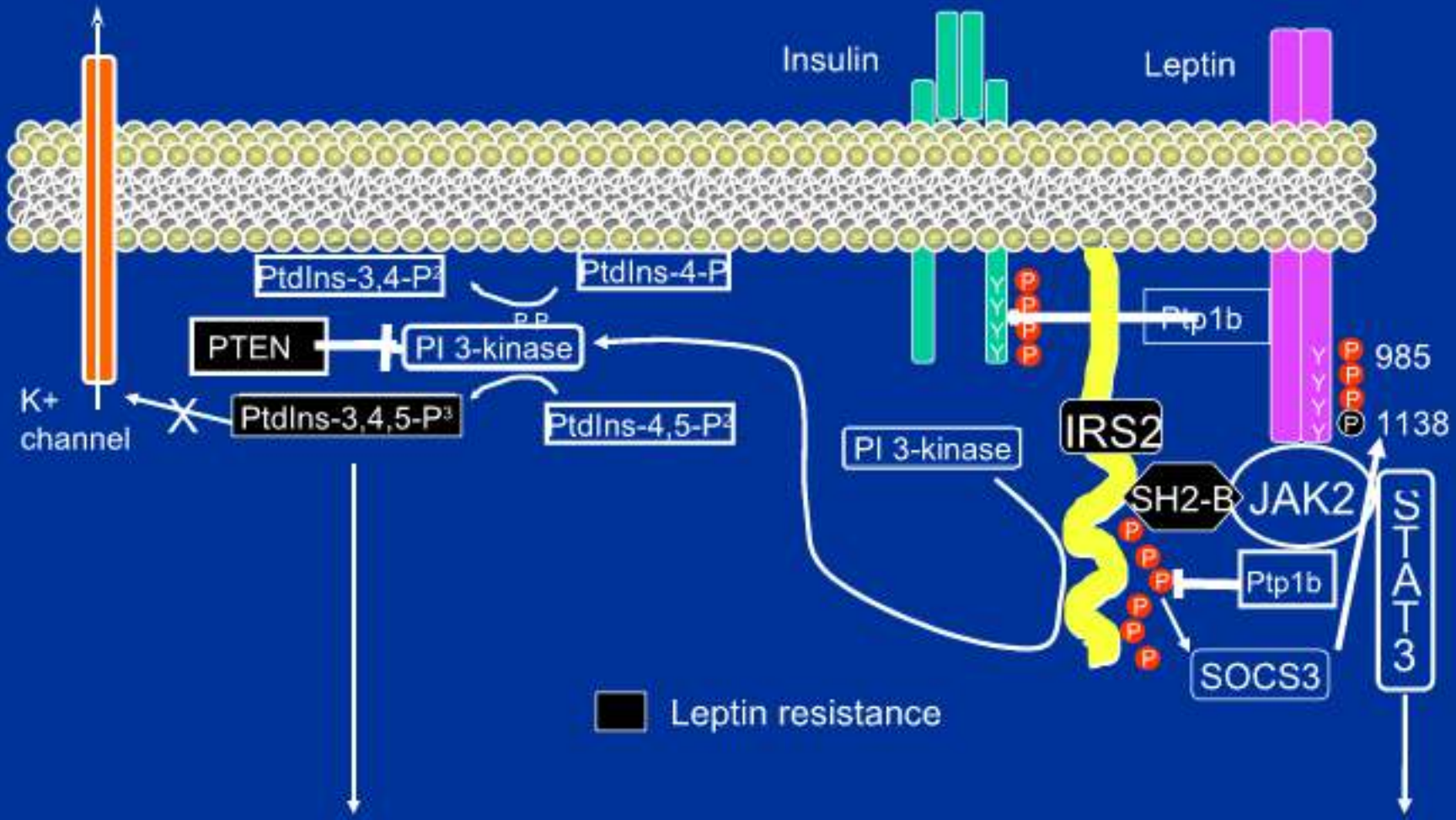

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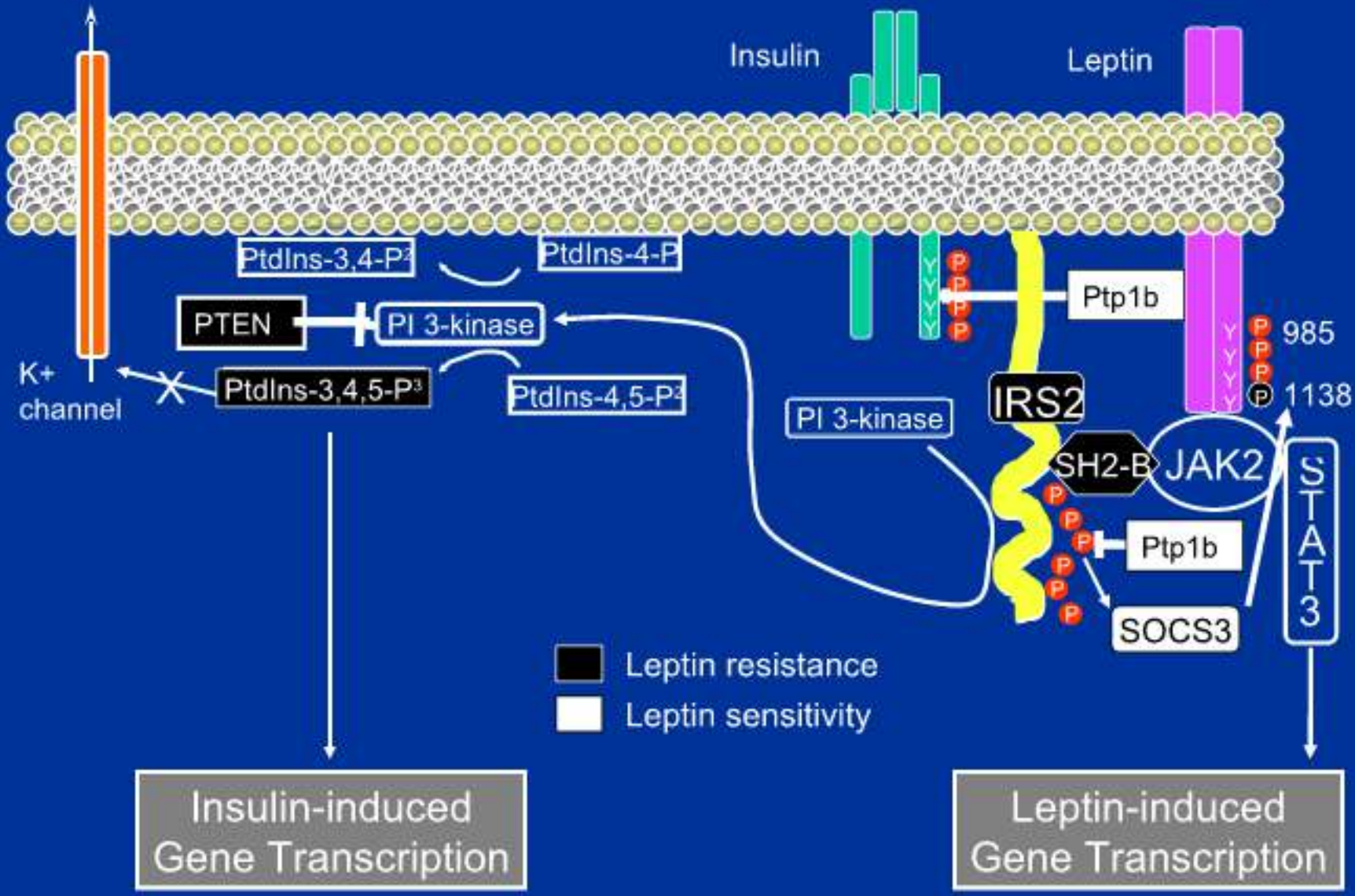
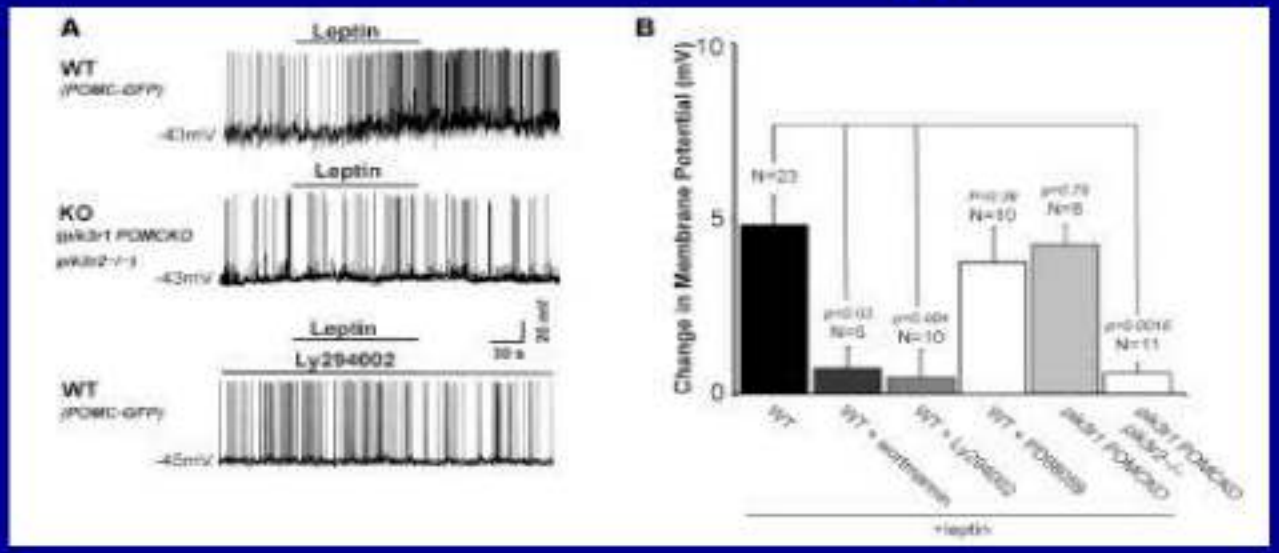
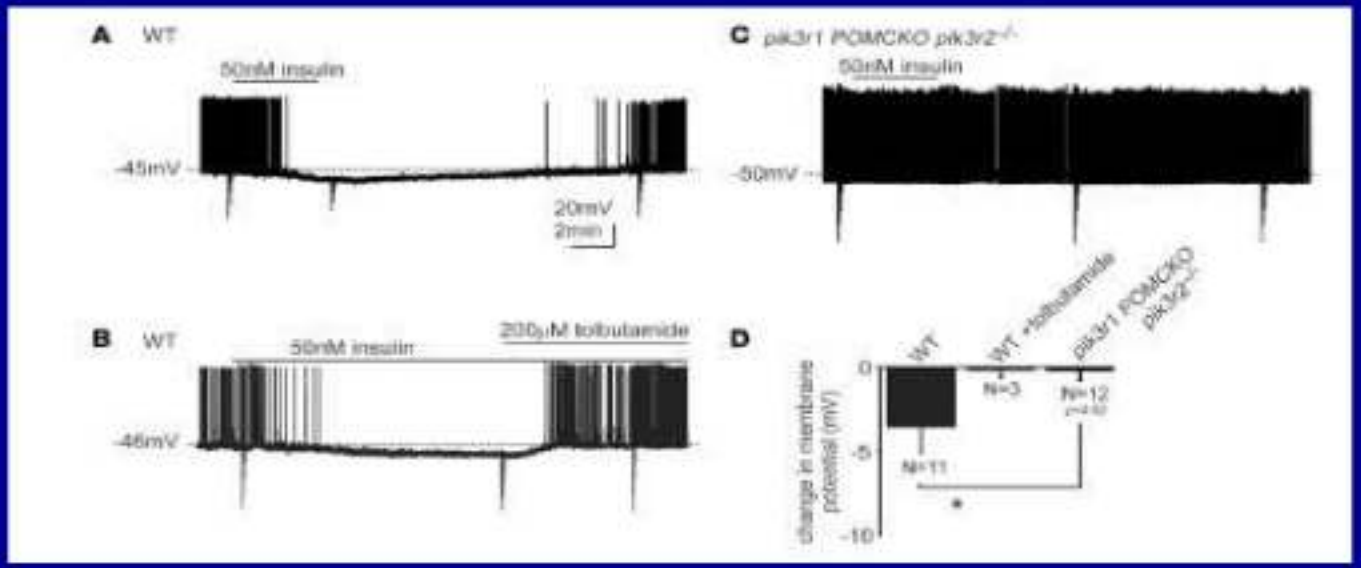


Lustig, Nature Clin Pract Endo Metab 2:447, 2006

Leptin depolarizes, while insulin hyperpolarizes POMC neurons through a PI3K-mediated mechanism





Hill et al. J Clin Invest 118:1796, 2008

Can hyperinsulinemia block leptin signaling?

Insulin inhibits leptin receptor signalling in HEK293 cells at the level of janus kinase-2: a potential mechanism for hyperinsulinaemia-associated leptin resistance

M. Kellerer[1], R. Lammers[1], A. Fritsche[1], V. Strack[1], E. Machicao[1], P. Borboni[3], A. Ullrich[2], H.U. Häring[1]

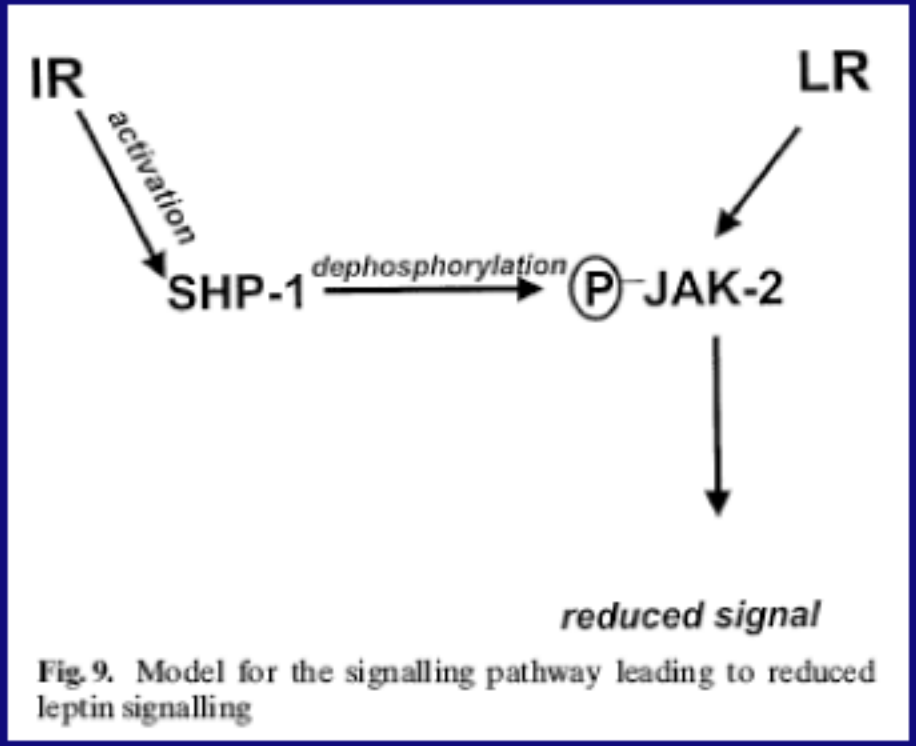
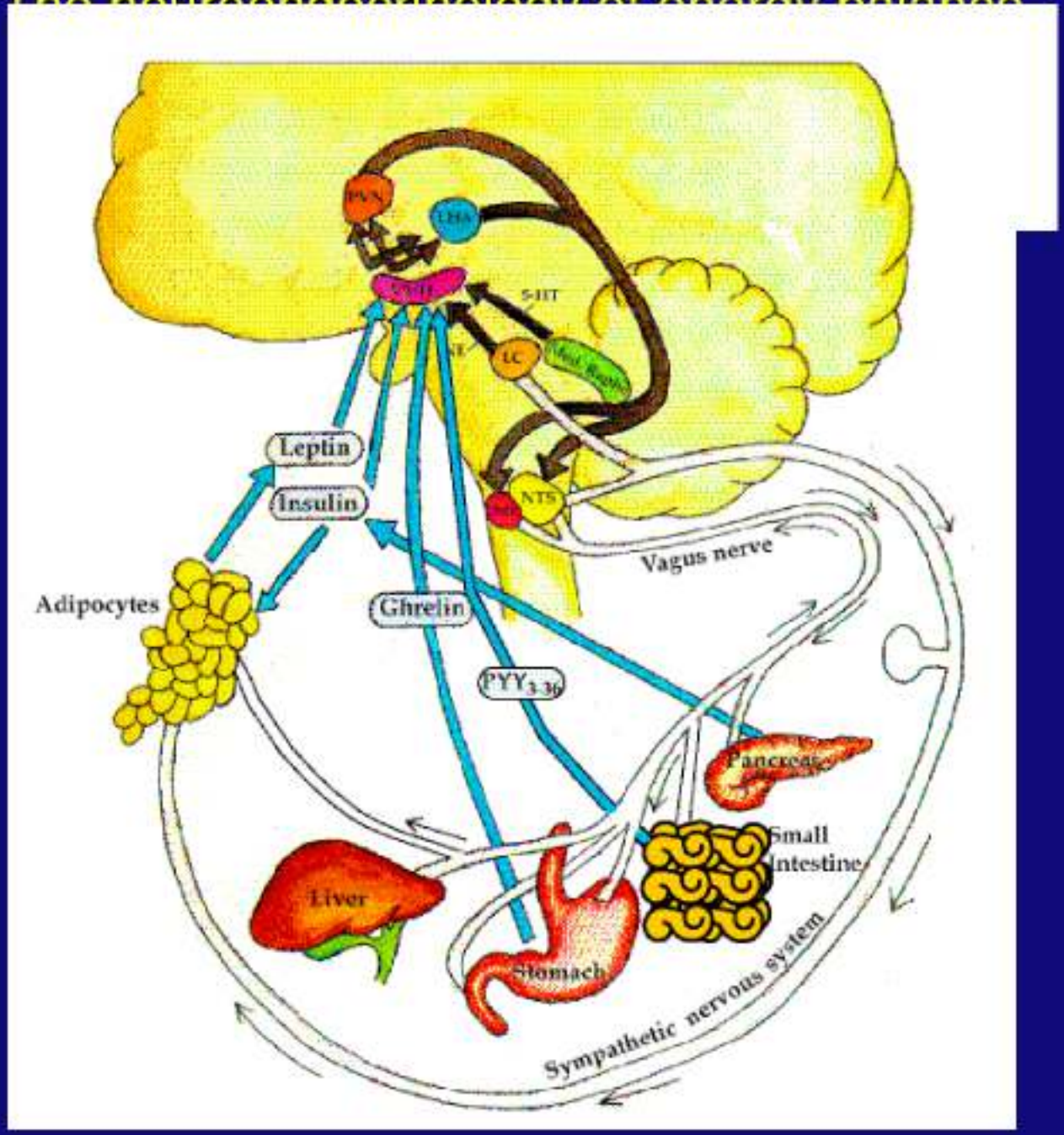


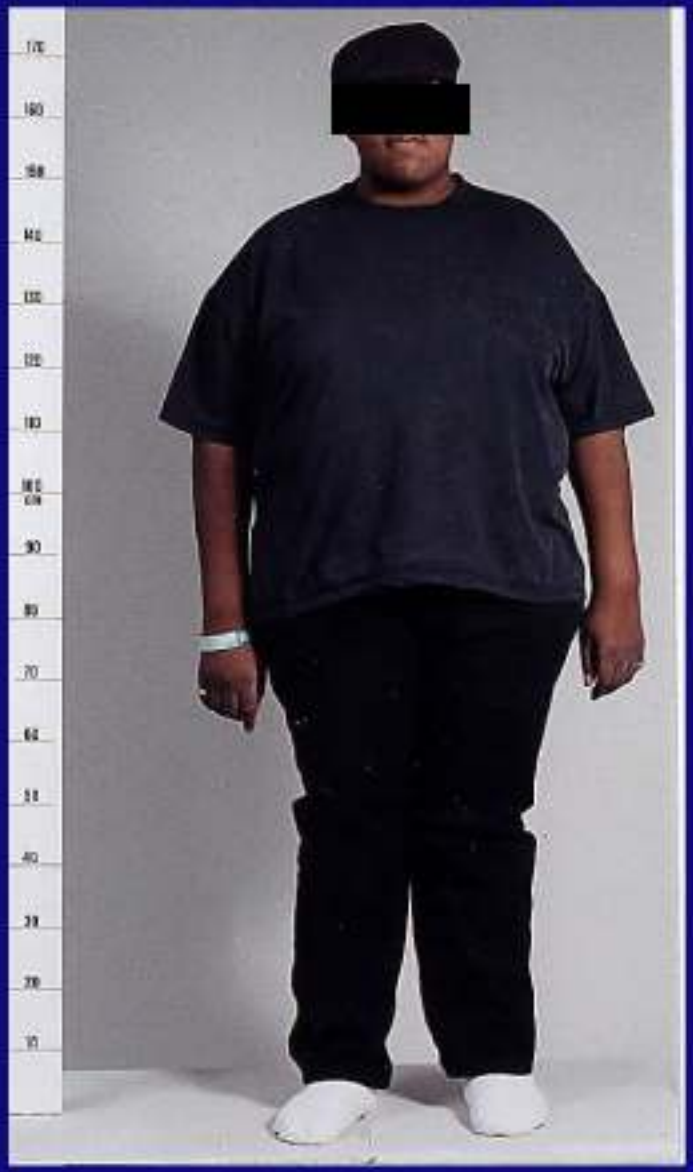
Fig. 9. Model for the signalling pathway leading to reduced leptin signalling

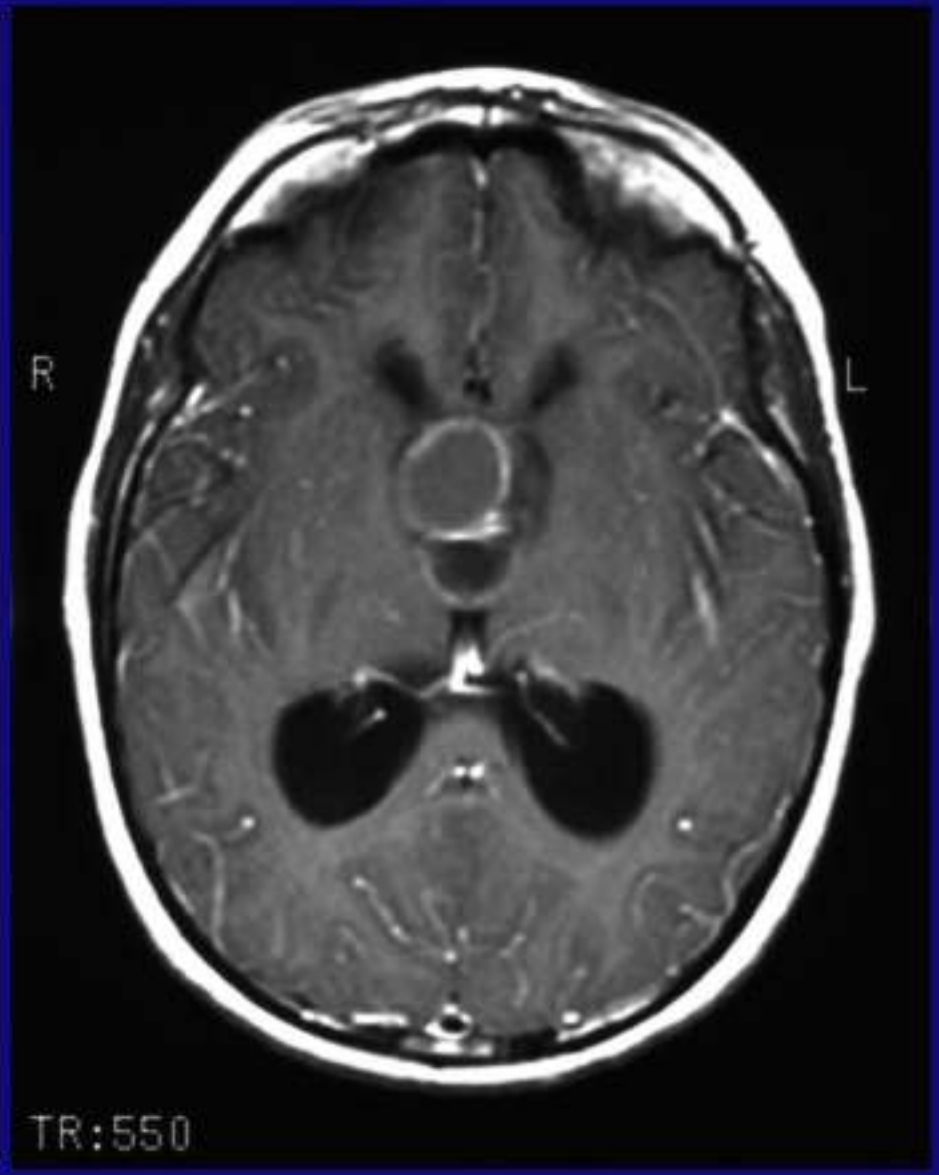
Kellerer et al. Diabetologia, 44:1125, 2001

The neuroendocrinology of energy balance



Anatomic leptin resistance:
Hypothalamic Obesity





Models/Hypotheses of Hypothalamic Obesity

Damaged Ventromedial Nucleus

↓

Hyperphagia

↓

Obesity

↓

Insulin Secretion

↓

IGF-I Receptor

↓

Growth

Adapted from
Sklar. *Pediatr Neurosurg.*
1994;21:120-123.

Damaged Ventromedial Nucleus

↓

Vagal Firing Rate

↓

Insulin Secretion

↓

Glucose Utilization

↓

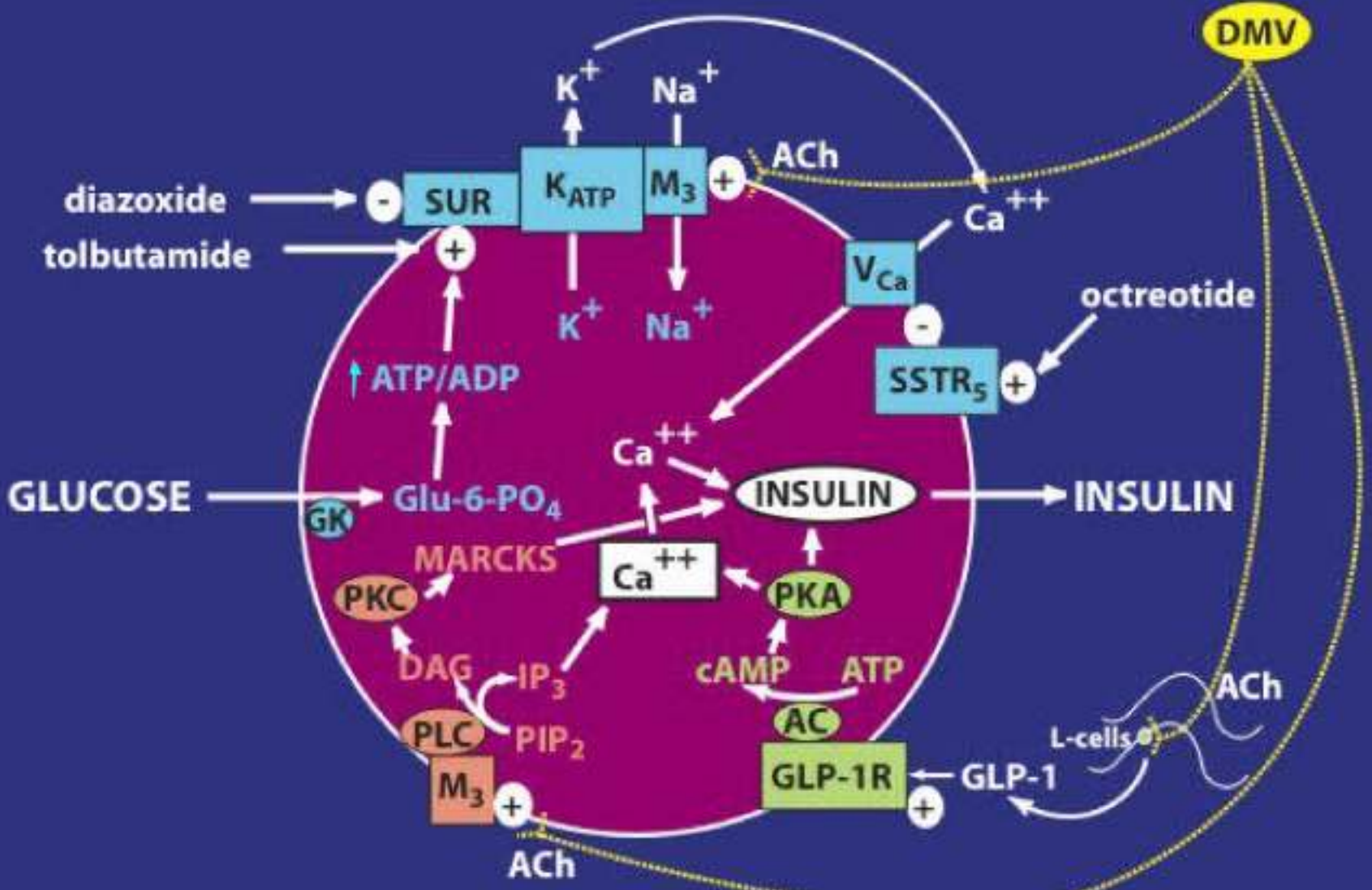
Hyperphagia

↓

Obesity

Adapted from
Bray and Gallagher. *Medicine*.
1975;54:301-330.

Vagal Modulation of Insulin Secretion

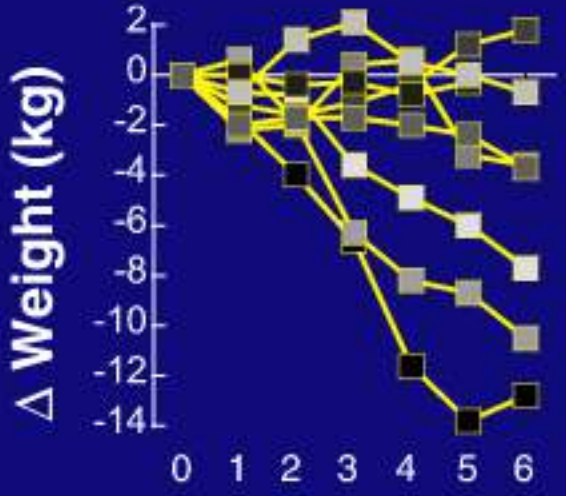


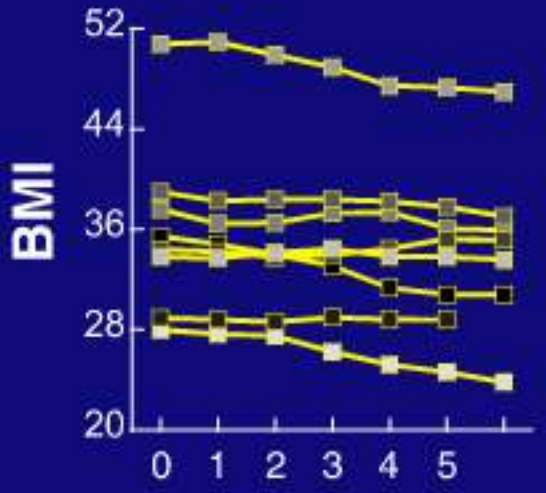
Lustig, Rev Endo Metab Dis 4:23, 2003

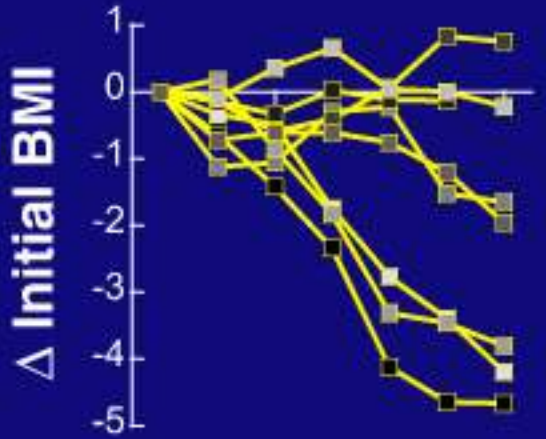
Hypothalamic Obesity Pilot Study—Purpose

1. To assess the insulin secretory dynamics of patients with hypothalamic obesity
2. To assess the efficacy of octreotide in reducing basal and glucose-stimulated insulin release in patients with hypothalamic obesity
3. To assess the efficacy of octreotide in promoting weight loss in patients with hypothalamic obesity

Hypothalamic Obesity Pilot Study—Weight and BMI Change

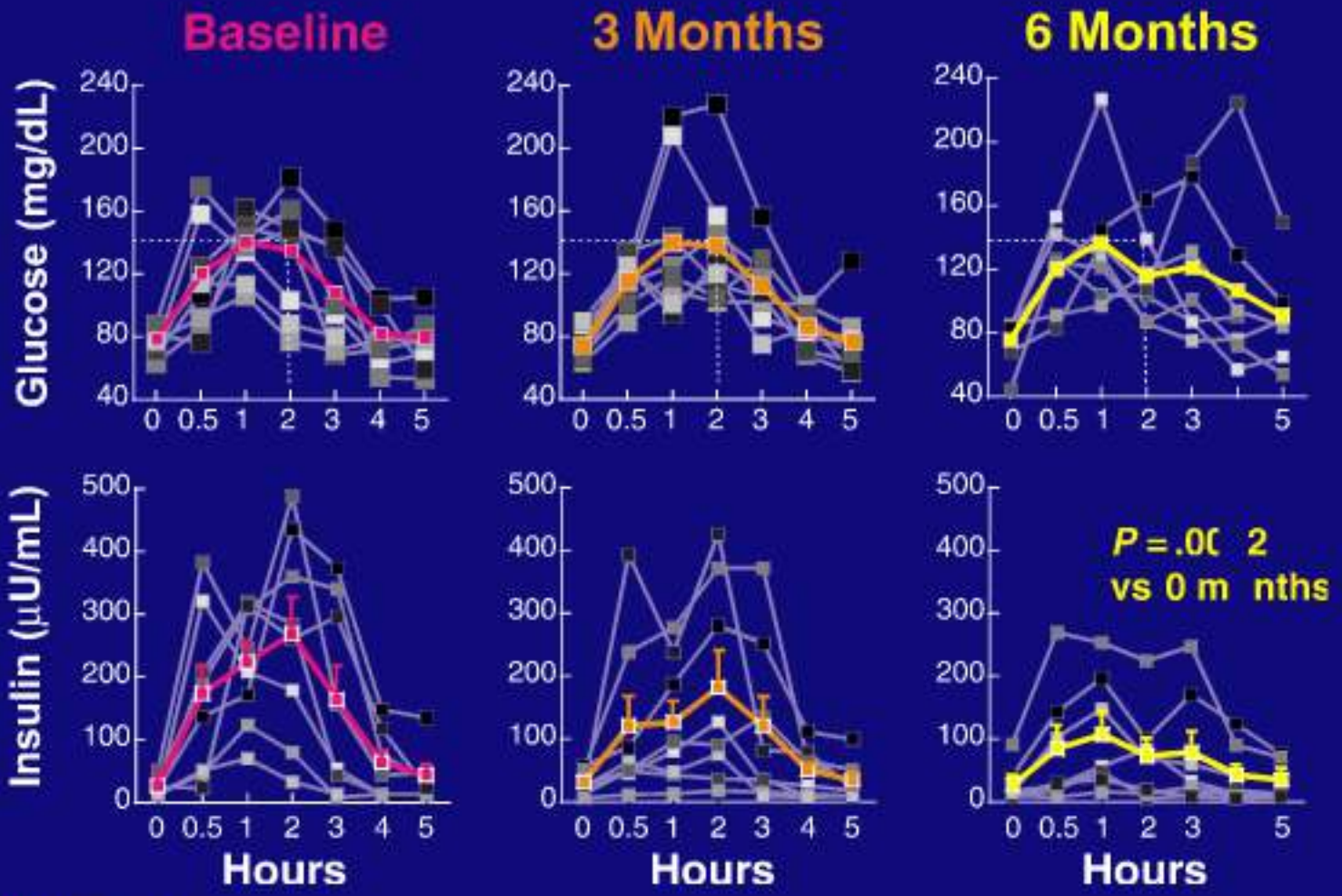






Lustig et al. J Pediatr 138:162, 1999

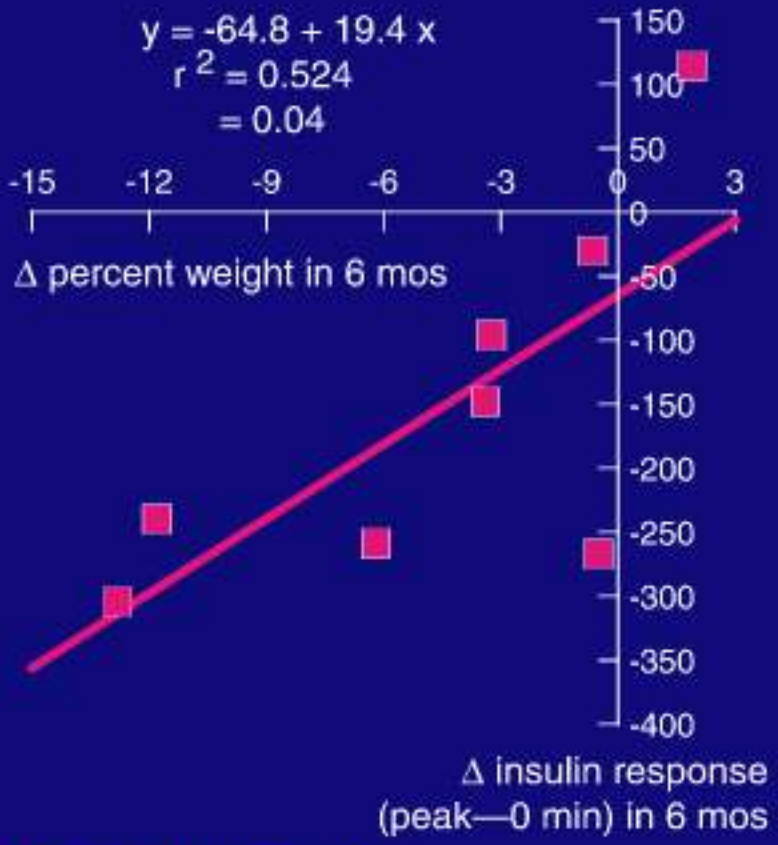
Hypothalamic Obesity Pilot Study— Effects on Glucose and Insulin Responses



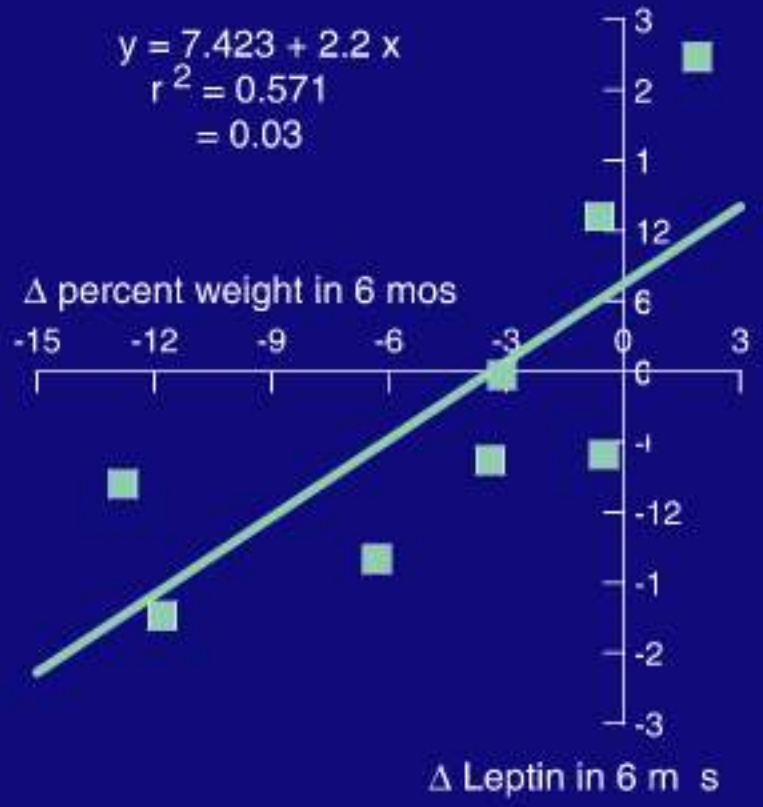
Lustig et al. J Pediatr 138:162, 1999

Hypothalamic Obesity Pilot Study—Weight Loss Versus:

Change in Insulin response on octreotide



Change in Leptin levels on octreotide



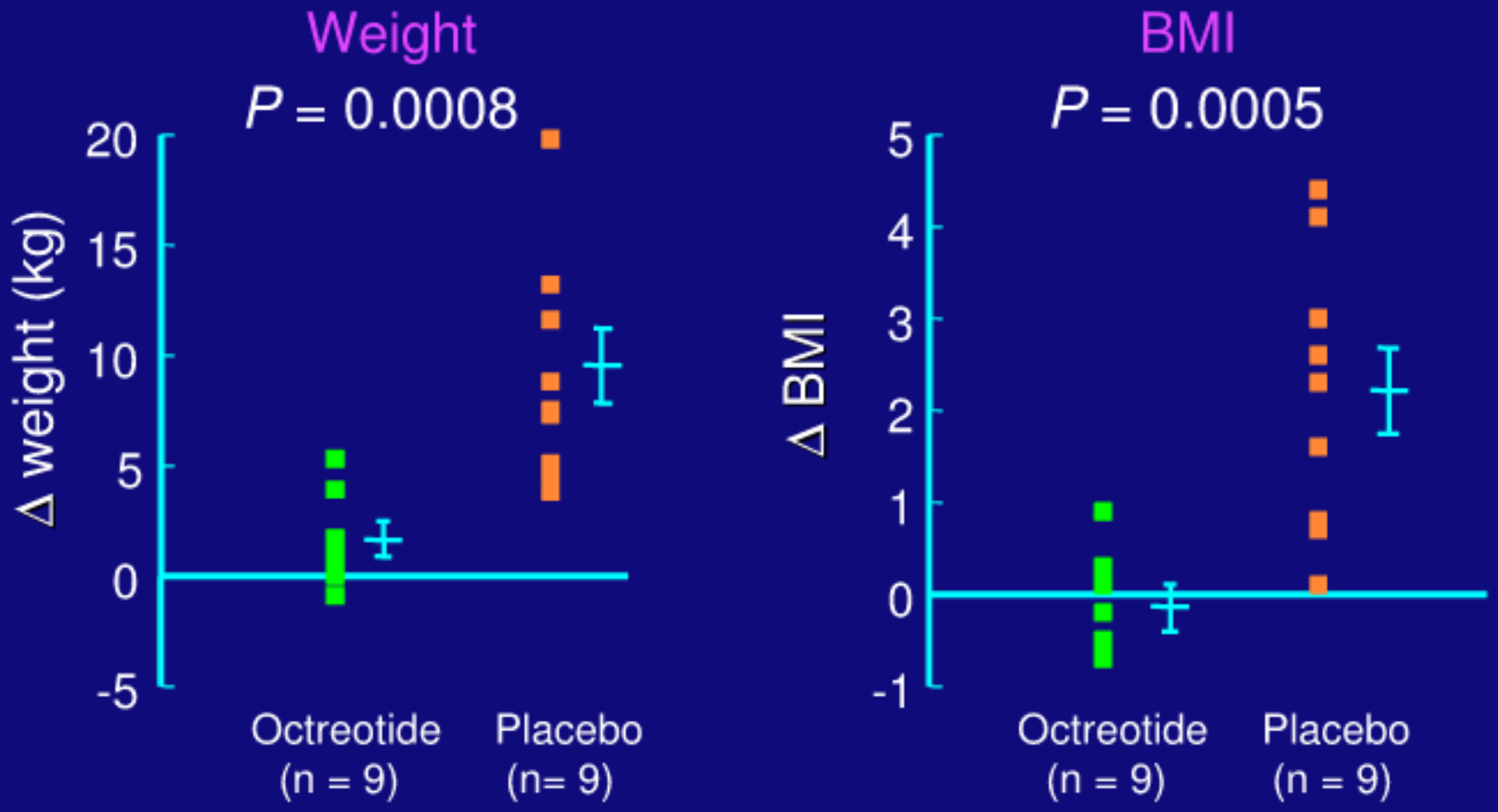
Lustig et al. J Pediatr 138:162, 1999

Octreotide treatment of hypothalamic obesity
Demographics

- Double-blinded, 6 month placebo-controlled trial of octreotide
- 20 subjects with pediatric hypothalamic obesity
  - ages 8-18; 11M, 9F
    - 2 from St. Jude
    - 18 from other institutions
  - 13 with craniopharyngioma
  - 4 with hypothalamic astrocytoma, optic pathway glioma
  - 1 with suprasellar germinoma
  - 2 with ALL, S/P cranial XRT and chemotherapy
- Weight 96.8 ± 5.7 kg, BMI 36.3 ± 1.3 kg/m2, annualized weight gain 15.9 ± 2.9 kg

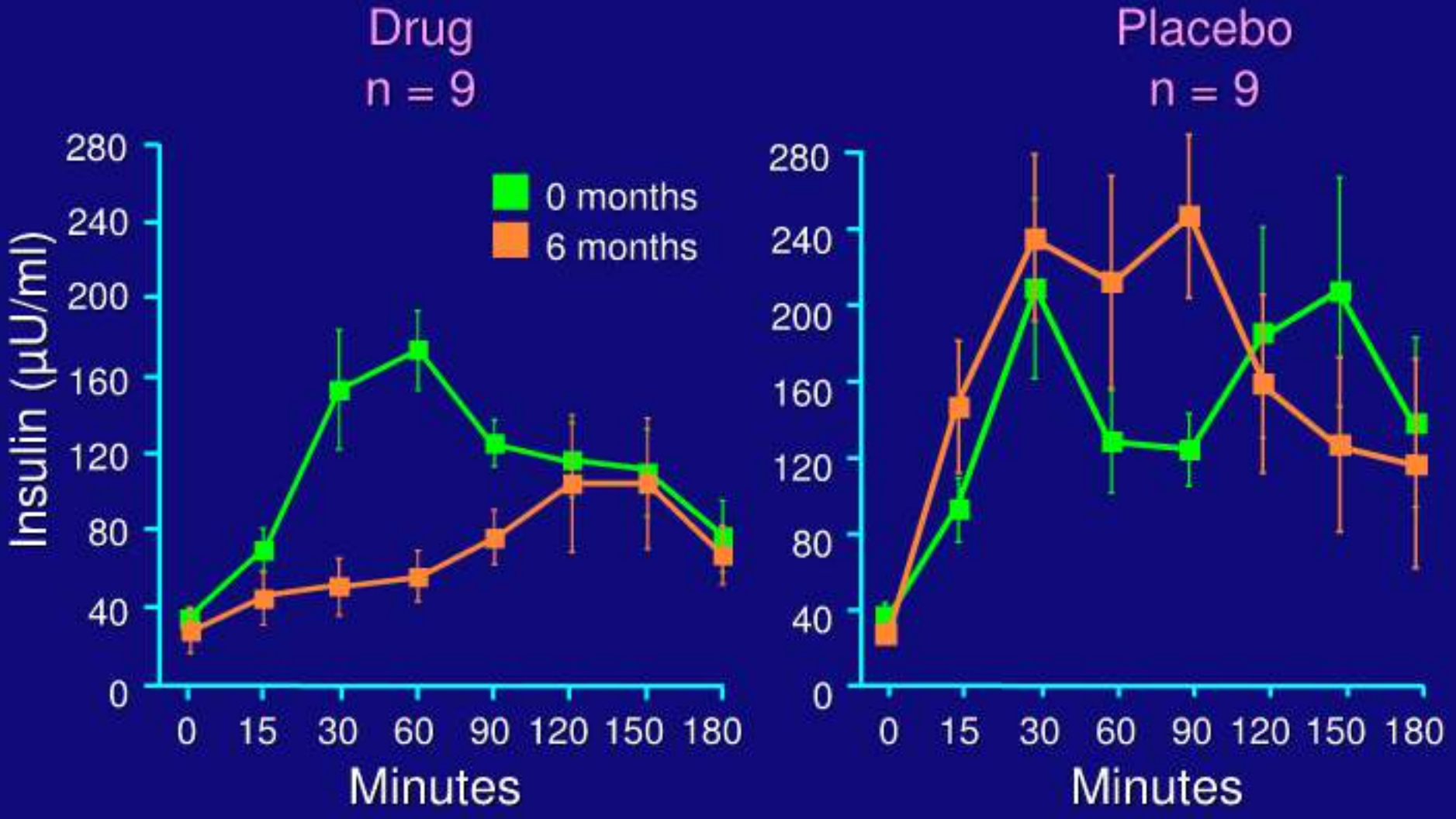
Lustig et al. JCEM 88:2586, 2003

Octreotide treatment of hypothalamic obesity
1st Window (6 Months)



Lustig et al. JCEM 88:2586, 2003

Octreotide treatment of hypothalamic obesity
Insulin dynamics during OGTT (1st Window)



Lustig et al. JCEM 88:2586, 2003

Pediatric Cancer Quality of Life PCQL-32, Version 1

32-item proctored questionnaire

Patient and parent reports on:

- Cognitive functioning
- Physical functioning
- Psychological functioning
- Social functioning

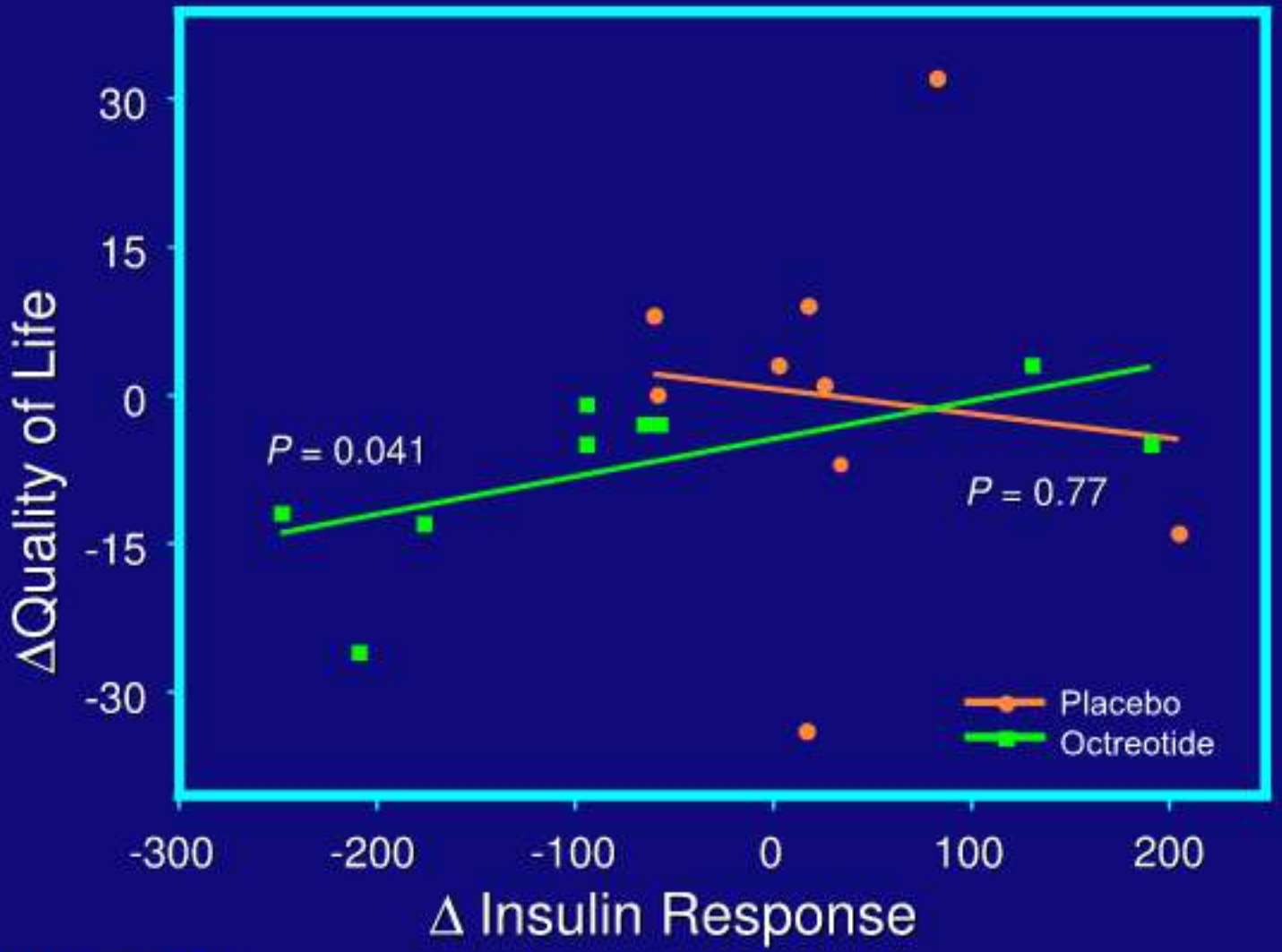
Validated for ages 8-18 yr

Octreotide Treatment of Hypothalamic Obesity
PCQL-32 (6 months – 0 months)

Functioning	Placebo		Octreotide		Intergroup	
	Child	Parent	Child	Parent	Child	Parent
Cognitive	0.33 NS	0.33 NS	0.22 NS	-1.33 NS	0.11 NS	1.67 NS
Physical	0.33 NS	0.78 NS	-1.44 NS	-2.22 *P*=0.05	1.78 NS	3.00 *P* =0.03
Psychological	0.11 NS	-0.11 NS	-1.89 *P* =0.09	-2.11 *P* =0.03	2.00 NS	2.00 NS
Social	0.22 NS	-1.22 NS	-1.89 *P* =0.09	-1.56 *P* =0.04	2.11 NS	0.33 NS

Lustig et al. JCEM 88:2586, 2003

PCQL-32 Parent Report
Correlation between ΔQuality of Life and Δ Insulin Response (6 Months – 0 Months)



Lustig et al. JCEM 88:2586, 2003

Patient #1

Before Octreotide
10/1/96

After 12 mos. Octreotide
10/1/97

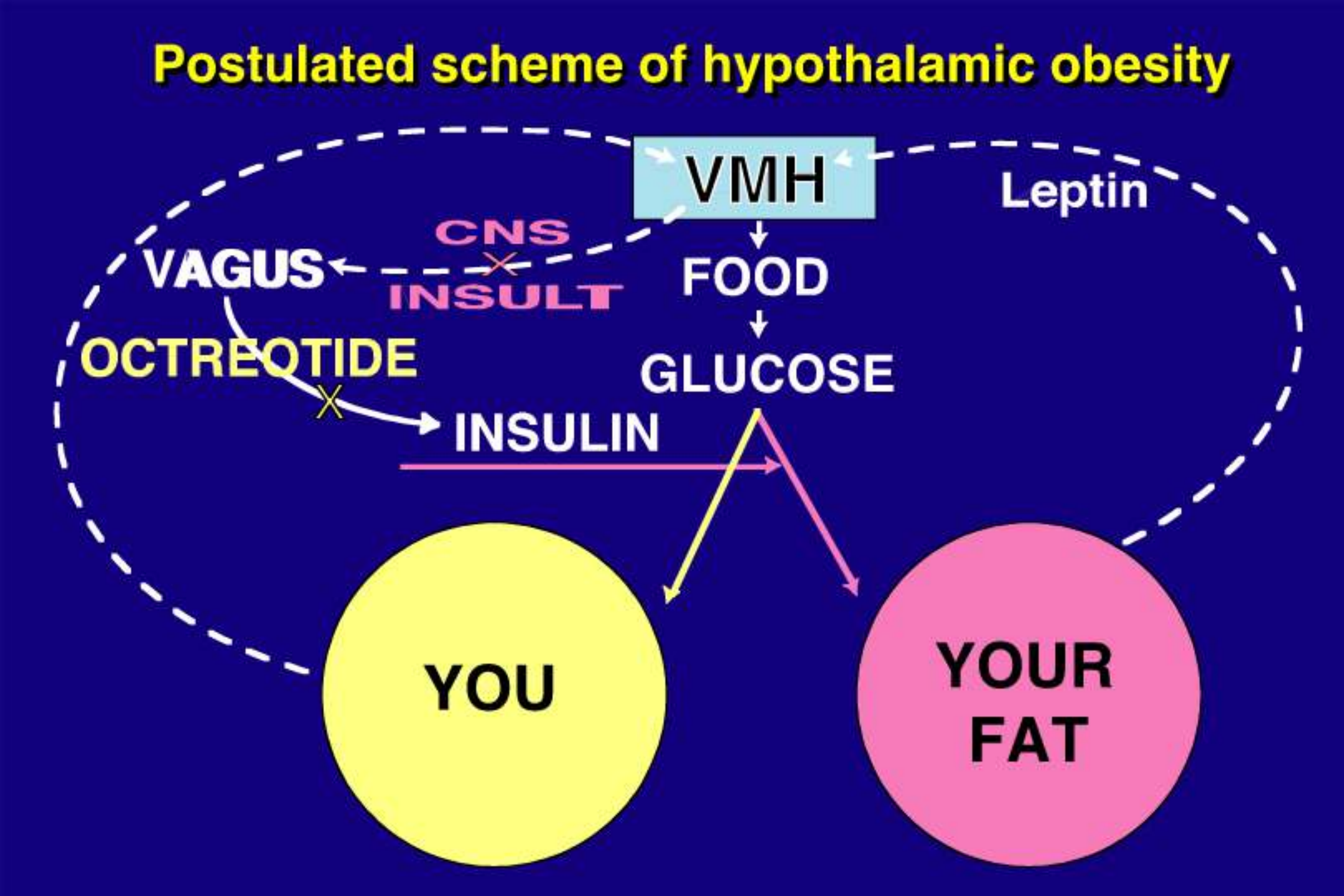
11/26/96 Age 10
Pre-Study
Wt 65.1 kg BMI 28.1

5/21/97 Age 10½
Octreotide x 6 mos.
Wt 57.4 kg BMI 23.9

9/10/99 Age 13
2¼ years post octreotide
Wt 90.4 kg BMI 34.4

Octreotide x 1 yr


SUPPORT THE
WILDLIFE


Postulated scheme of hypothalamic obesity
VMH
Leptin
CNS
VAGUS
INSULT
FOOD
OCTREOTIDE
GLUCOSE
INSULIN
YOU
YOUR FAT

Functional studies of leptin resistance: Octreotide for adult obesity

Hypotheses:

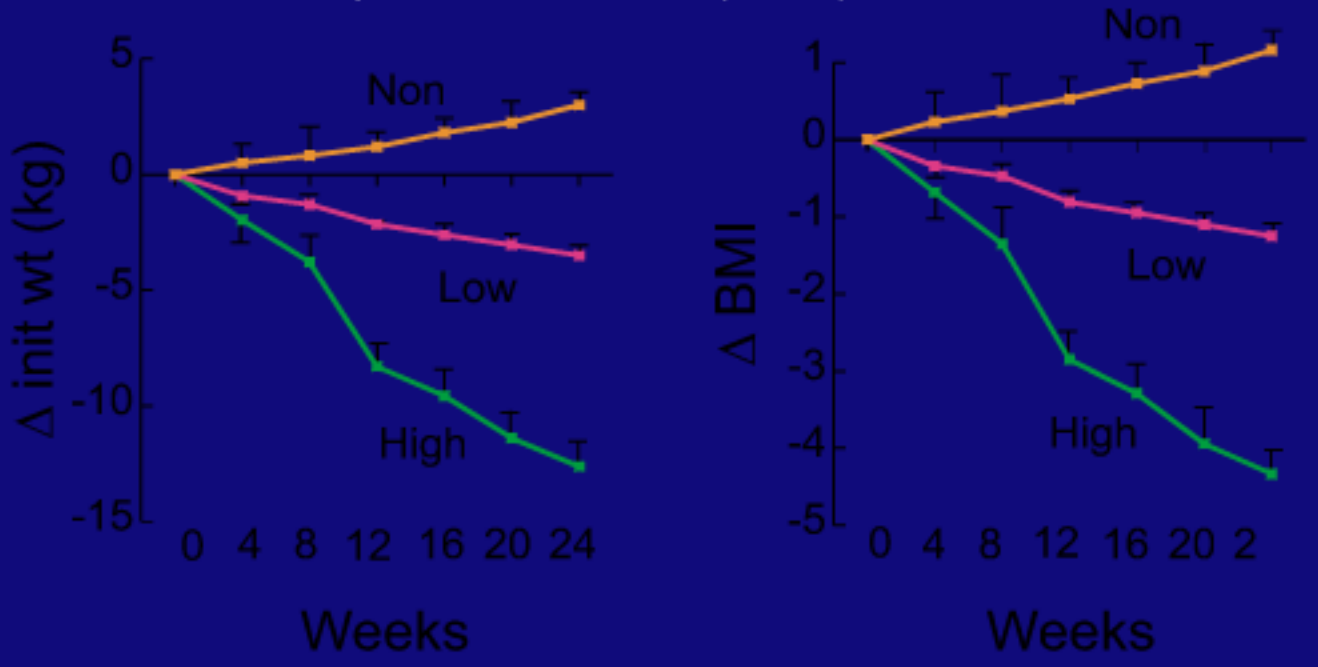
Insulin hypersecretion occurs in a subset of obese adults

Insulin suppression using octreotide will

- Slow or reverse adipogenesis
- Promote weight loss

Octreotide-LAR 40 mg IM q 28d
Effects on Weight and BMI Stratified By Response

Patients who completed 24 weeks (n=44)



Weight Response:

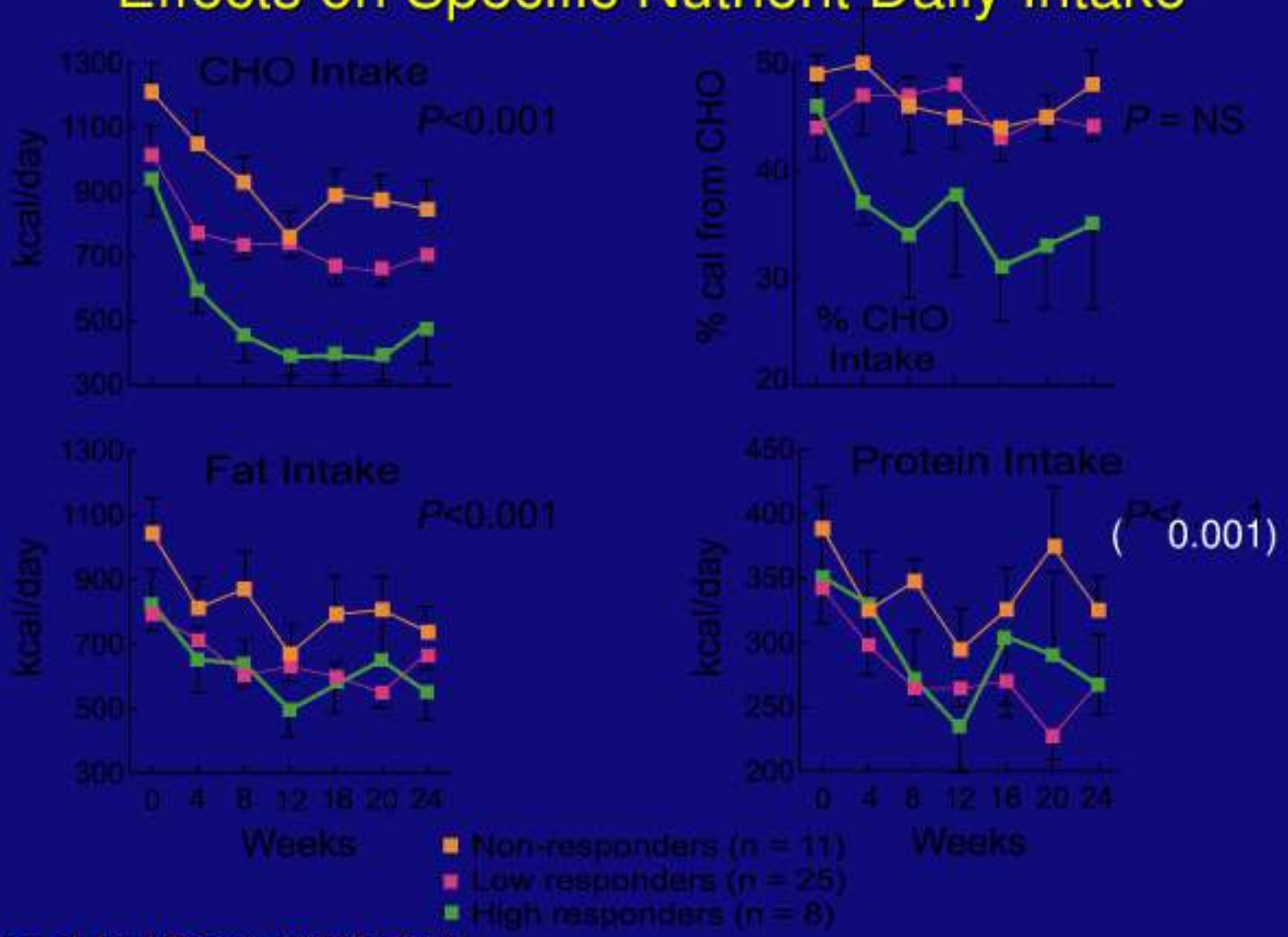
- Non-responders (Δ BMI > 0) (n = 11)
- Low responders (-3 < Δ BMI < 0) (n = 25)
- High responders (Δ BMI < -3) (n = 8)

P< 0.0001

ANOVA with repeated measures

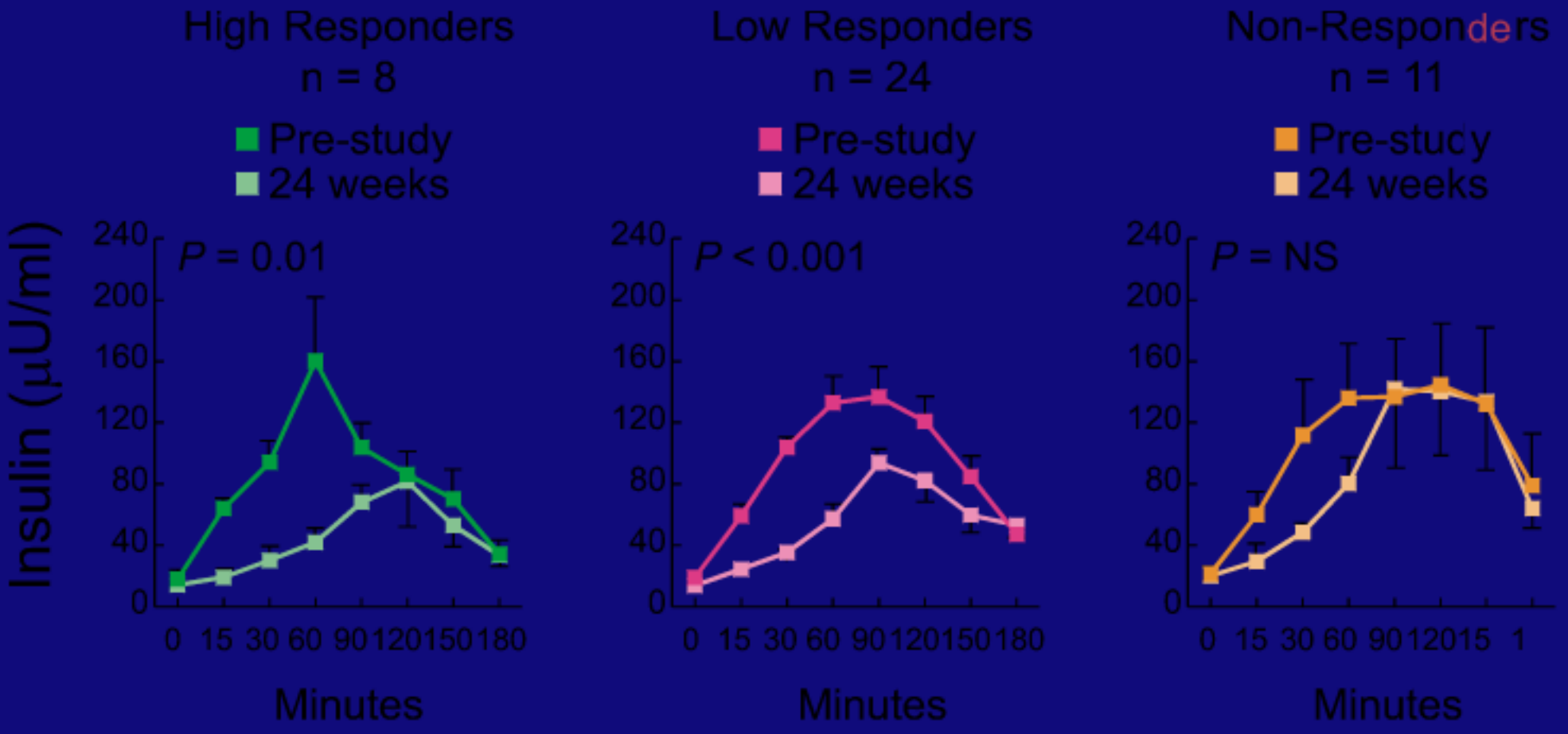
Velasquez-Mieyer et al. Int J Obesity 27:216, 2003

Octreotide-LAR 40 mg IM q28d
Effects on Specific Nutrient Daily Intake



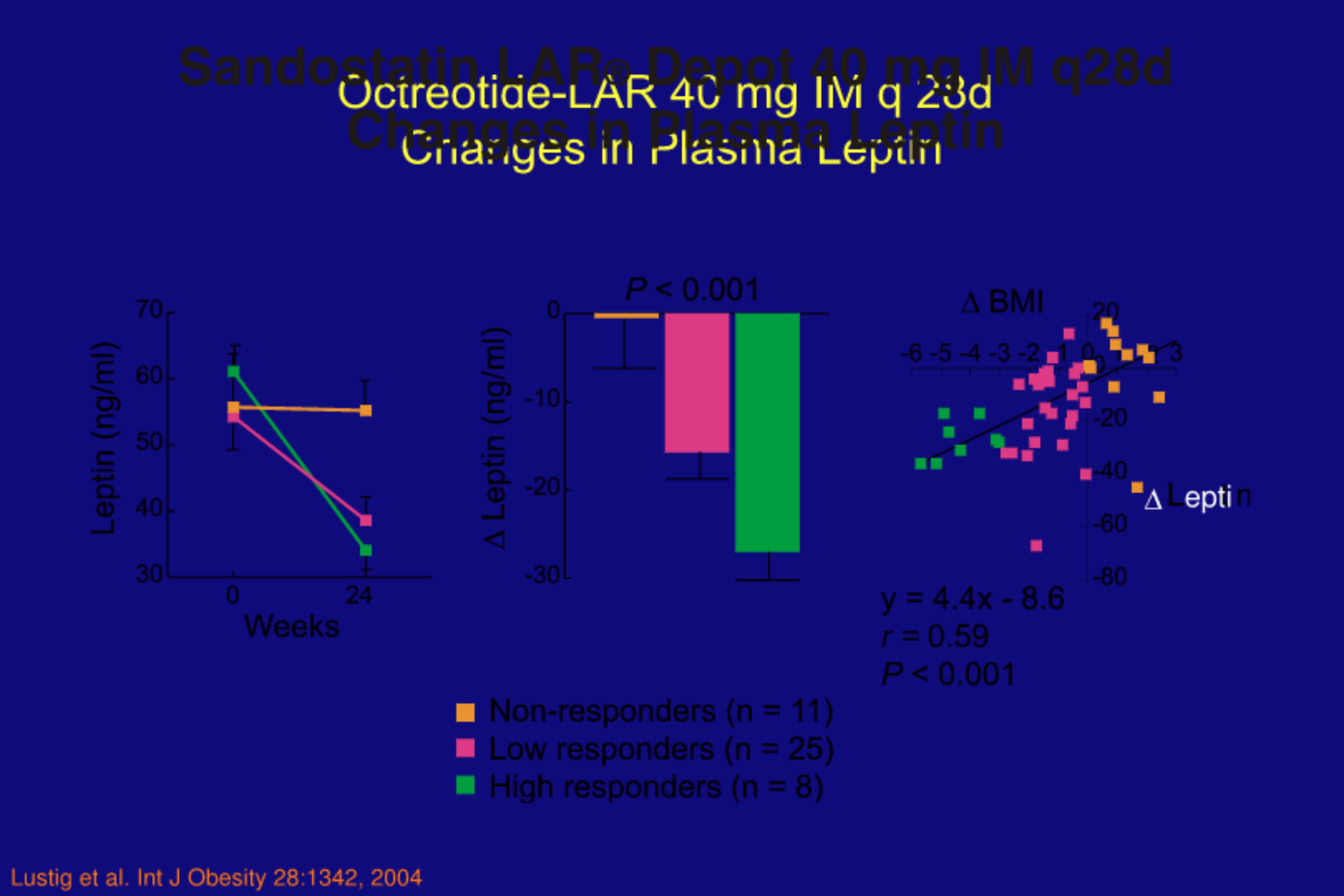
Velasquez-Mieyer et al. Int J Obesity 27:216, 2003

Octreotide-LAR 40 mg IM q 28d
Insulin Dynamics During OGTT



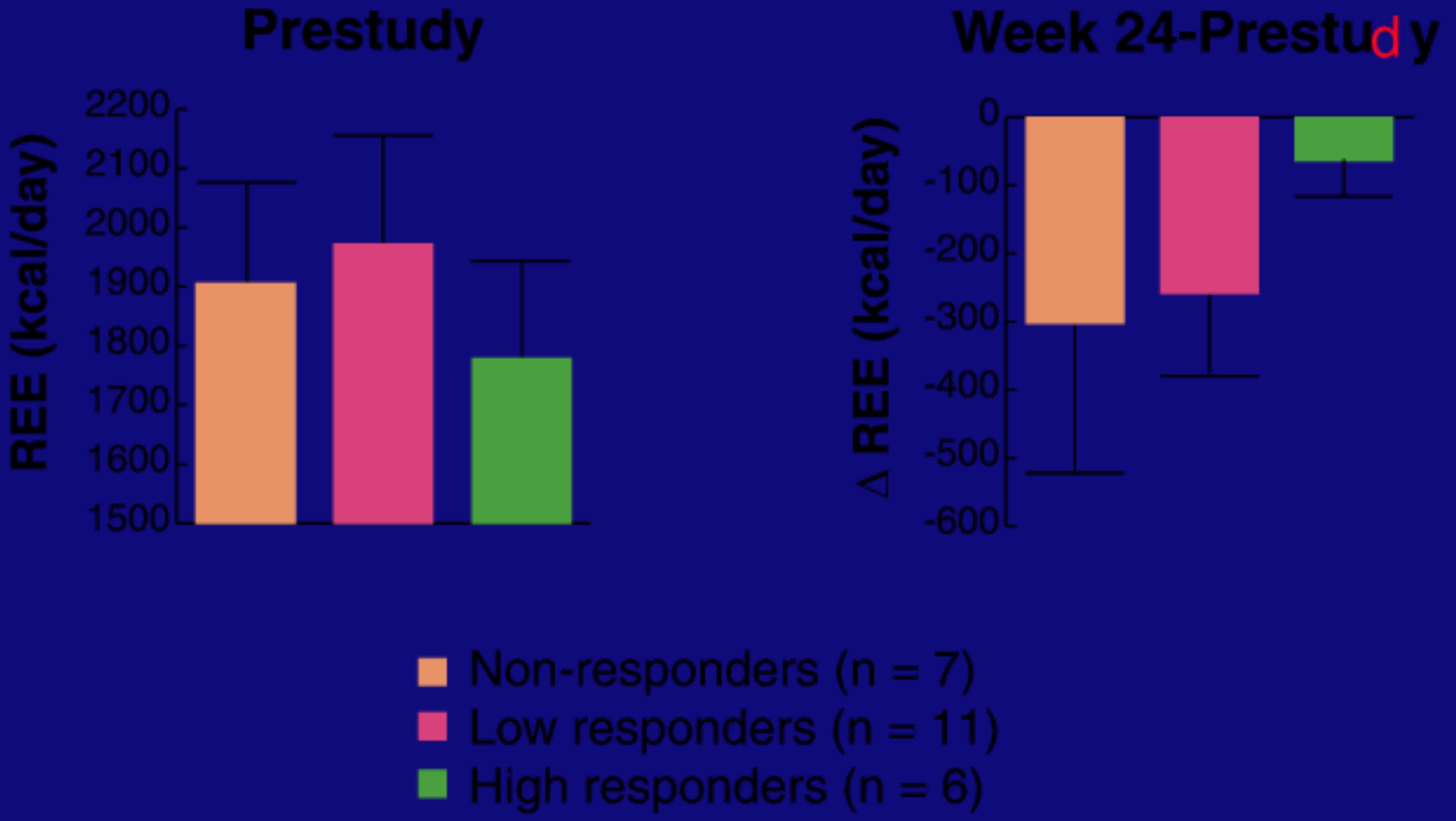
Velasquez-Mieyer et al. Int J Obesity 27:216, 2003

Sandostatin LAR® Depot 40 mg IM q28d
Changes in Plasma Leptin



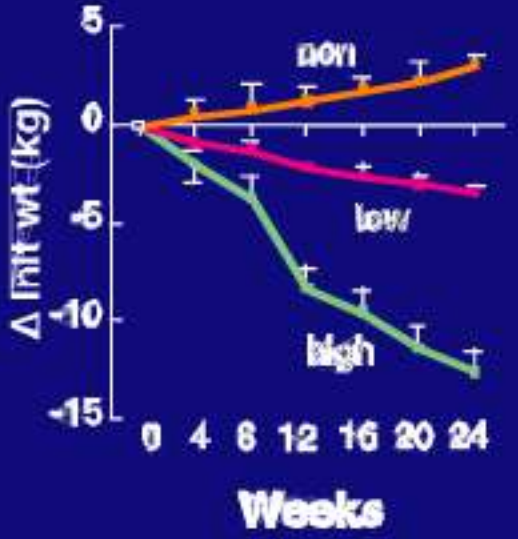
Lustig et al. Int J Obesity 28:1342, 2004

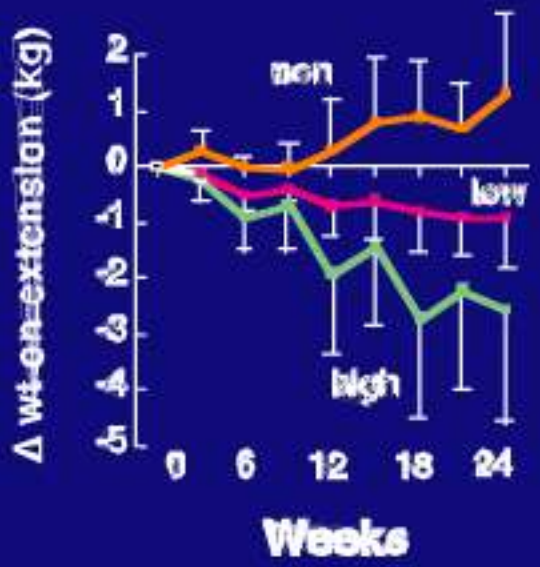
Octreotide-LAR 40 mg IM q28d
Changes in Resting Energy Expenditure (REE)

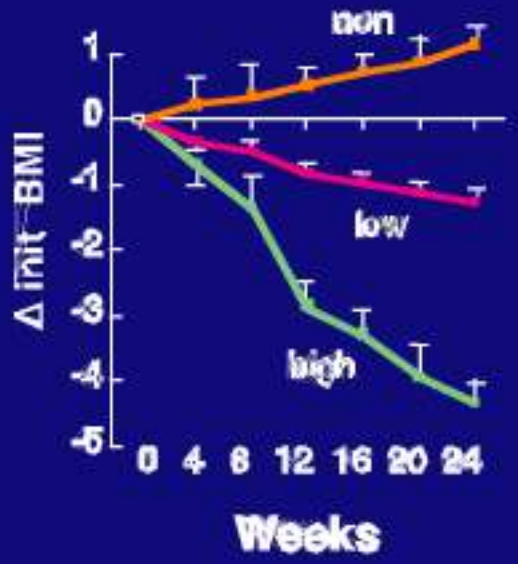


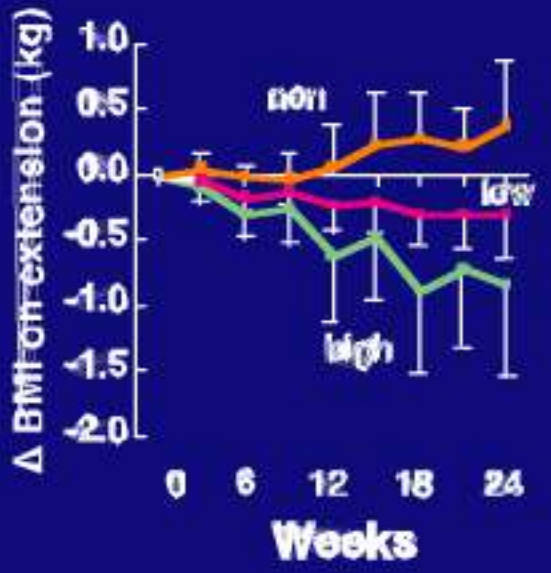
Lustig et al. Int J Obesity 28:1342, 2004

Octreotide-LAR 40 mg IM q 21d: 6 month extension
Effects on Weight and BMI stratified by response









High Responders

No.	Wt loss 24 weeks	Wt loss 48 weeks
6	-14.51	-21.81
12	-9.63	-7.23
13	-8.86	
25	-10.34	-9.24
29	-17.77	-25.47
31	-11.44	-8.24
33	-15.03	-22.13
42	-13.80	
Mean	-12.61	-15.69

Octreotide-LAR x 6 months

Improvement of functional leptin sensitivity

- Forced weight loss (Rosenbaum)
- Drug-induced reduction in insulin (Lustig)

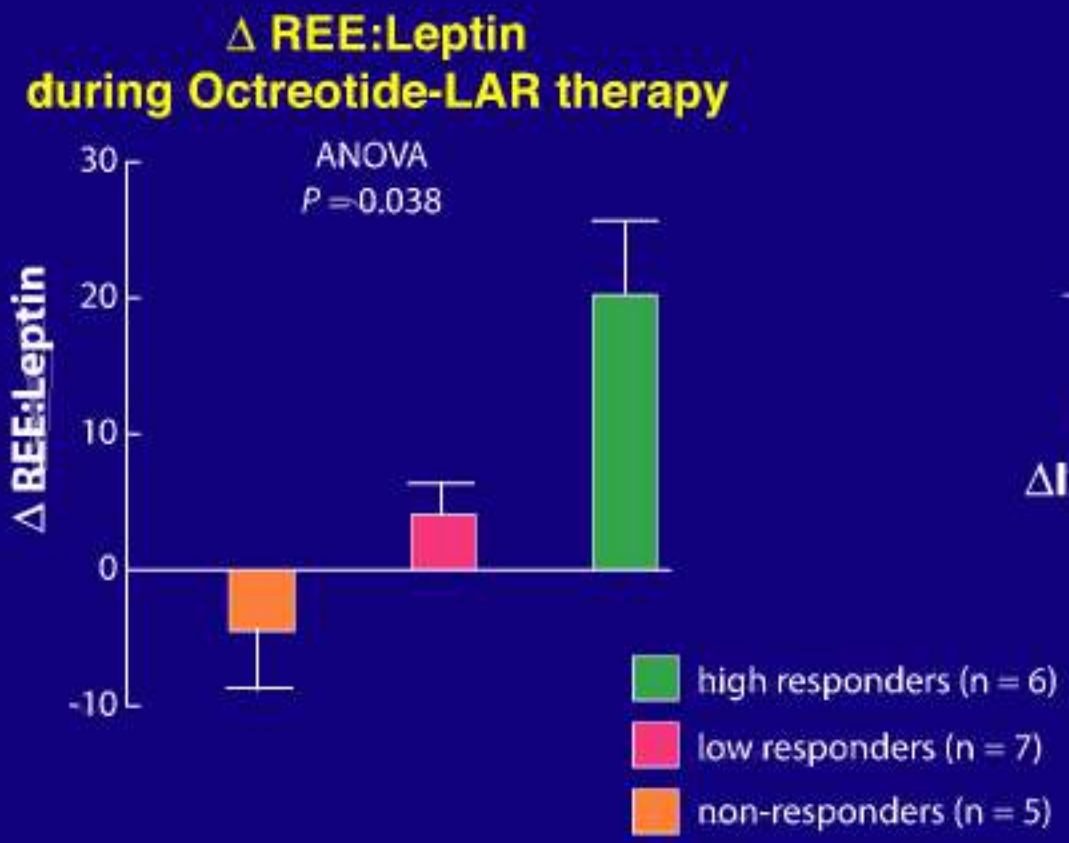
Improvement of functional leptin sensitivity

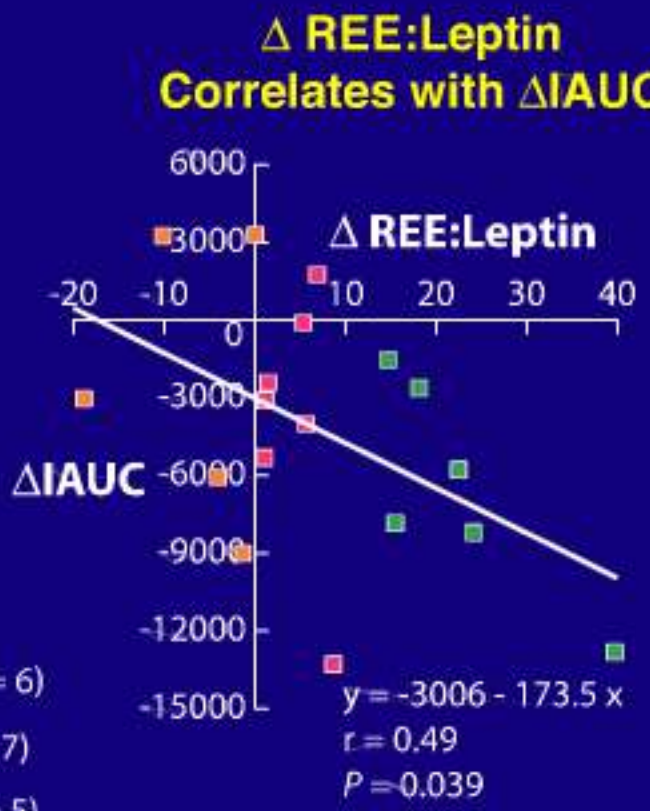
- Forced weight loss (Rosenbaum)
- Drug-induced reduction in insulin (Lustig)

What's the similarity?

The drop in insulin

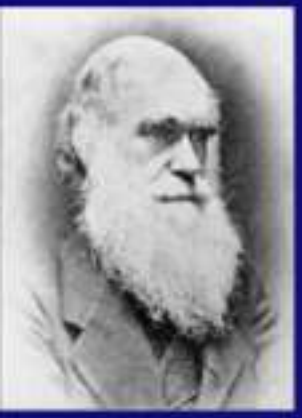
Octreotide-LAR 40 mg IM q28d
Changes in the REE:Leptin Ratio





Lustig et al. Int J Obesity 28:1342, 2004

Insulin is an endogenous leptin antagonist (?)

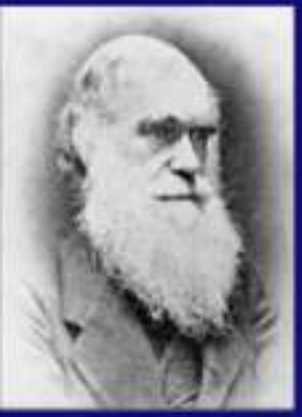


Insulin is an endogenous leptin antagonist (?)

Does this make Darwinian sense?

Insulin gives the human the ability to modulate weight gain acutely, by allowing hyperinsulinemia to induce leptin resistance:

1. Puberty
2. Pregnancy



Insulin is an endogenous leptin antagonist (?)

Does this make Darwinian sense?

Insulin gives the human the ability to modulate weight gain acutely, by allowing hyperinsulinemia to induce leptin resistance:

1. Puberty
2. Pregnancy

Doesn't it make sense that the same hormone that promotes the energy storage also inhibits leptin, so that energy can be stored?

Where did the hyperinsulinemia come from?

- Genetics

i.e. VNTR of insulin gene

- Epigenetics

i.e. SGA, LGA promote insulin resistance

- Social Environment (cortisol)

i.e. economic (food insecurity), acculturation, violence, other societal stressors

- Exercise Environment

i.e. cars; lack of sidewalks, play areas, school activity

- Food Environment

i.e. fructose (too much), fiber (not enough)

Causes insulin resistance, hyperinsulinemia

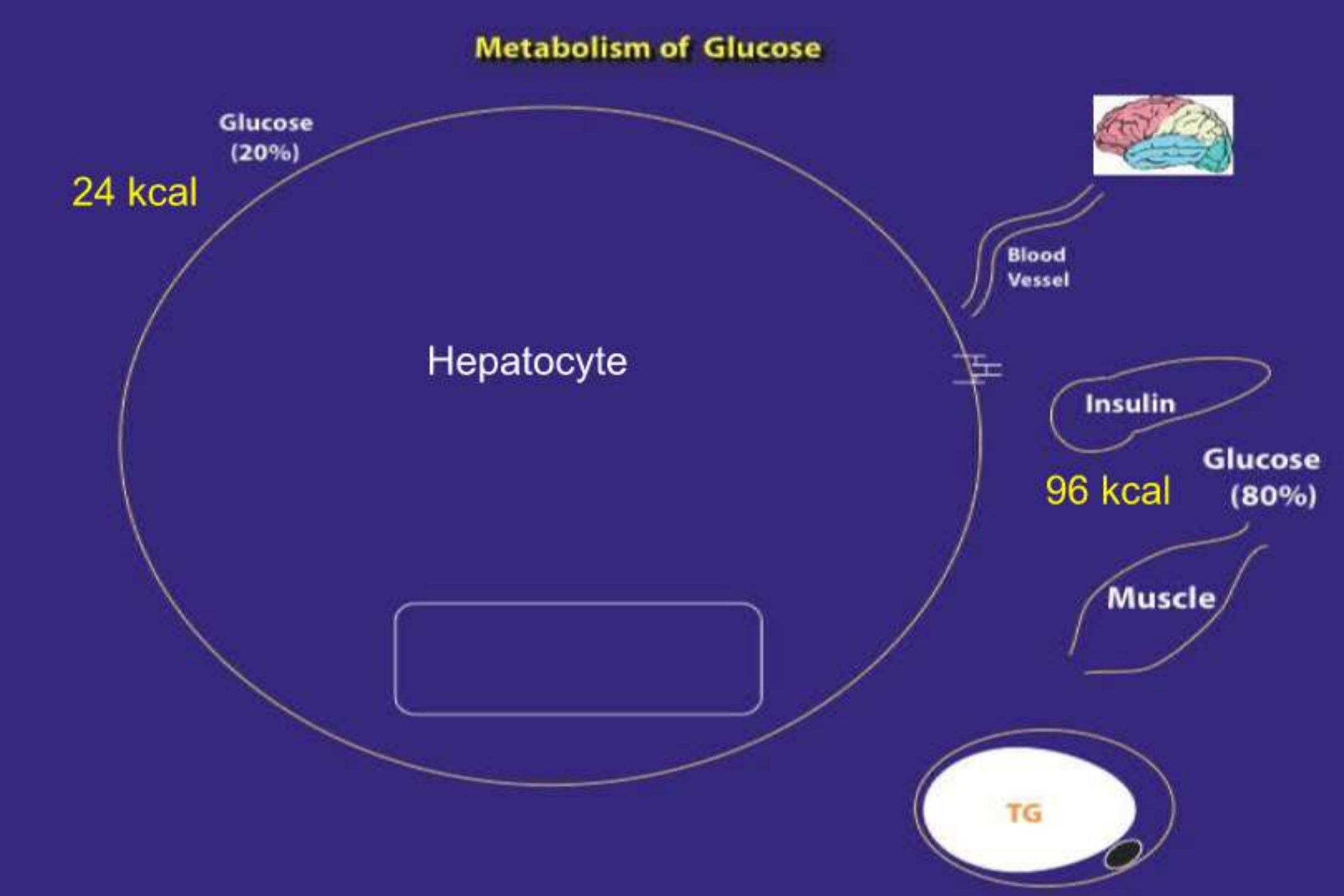
Fructose is not glucose

- Hepatic fructose metabolism is different than glucose
- Hypothesis: chronic fructose exposure promotes NAFLD and Metabolic Syndrome

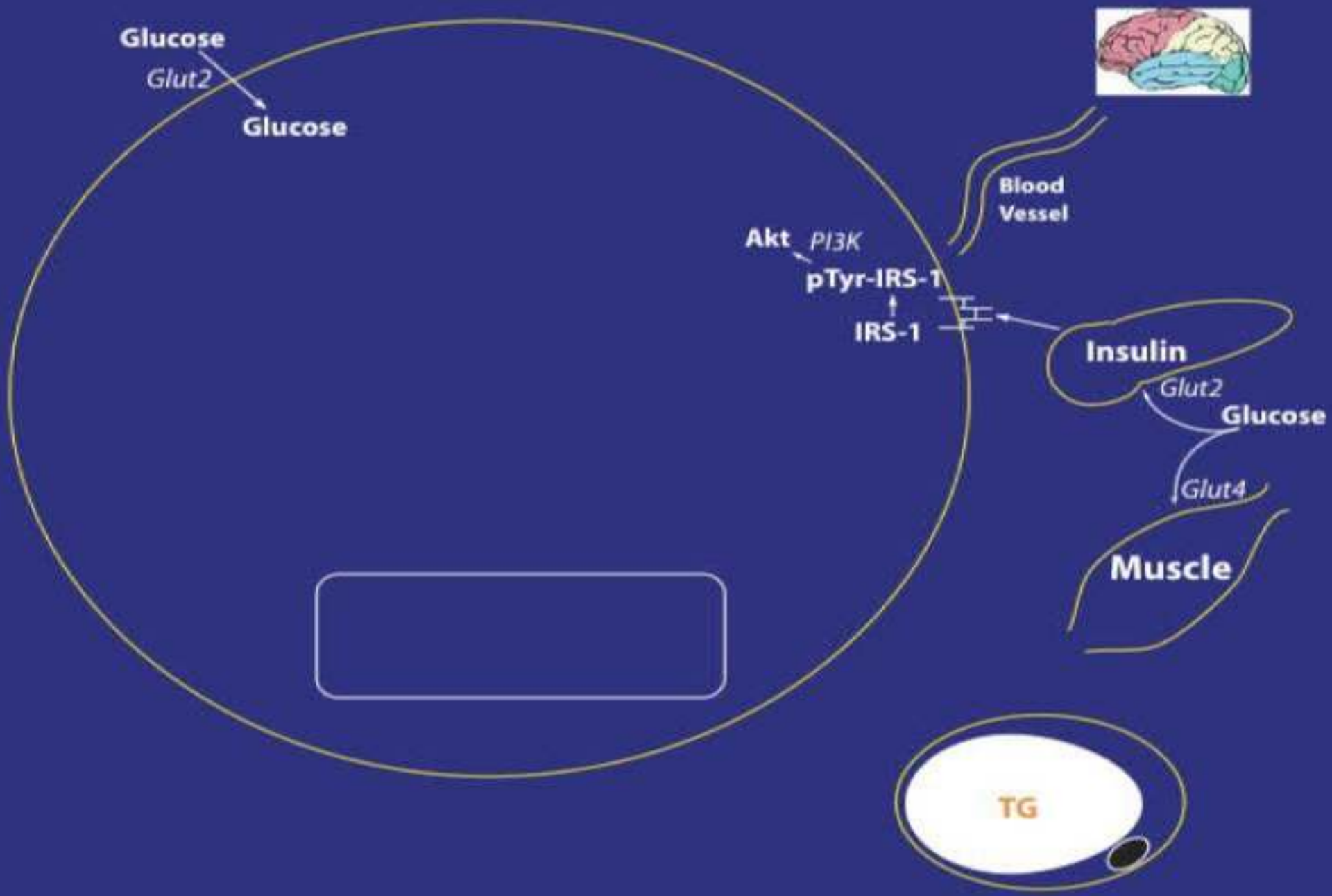
Elliot et al. Am J Clin Nutr, 2002
Bray et al. Am J Clin Nutr, 2004
Teff et al. J Clin Endocrinol Metab, 2004
Gaby, Alt Med Rev, 2005

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
Collison et al. Obesity epub 3/12/09

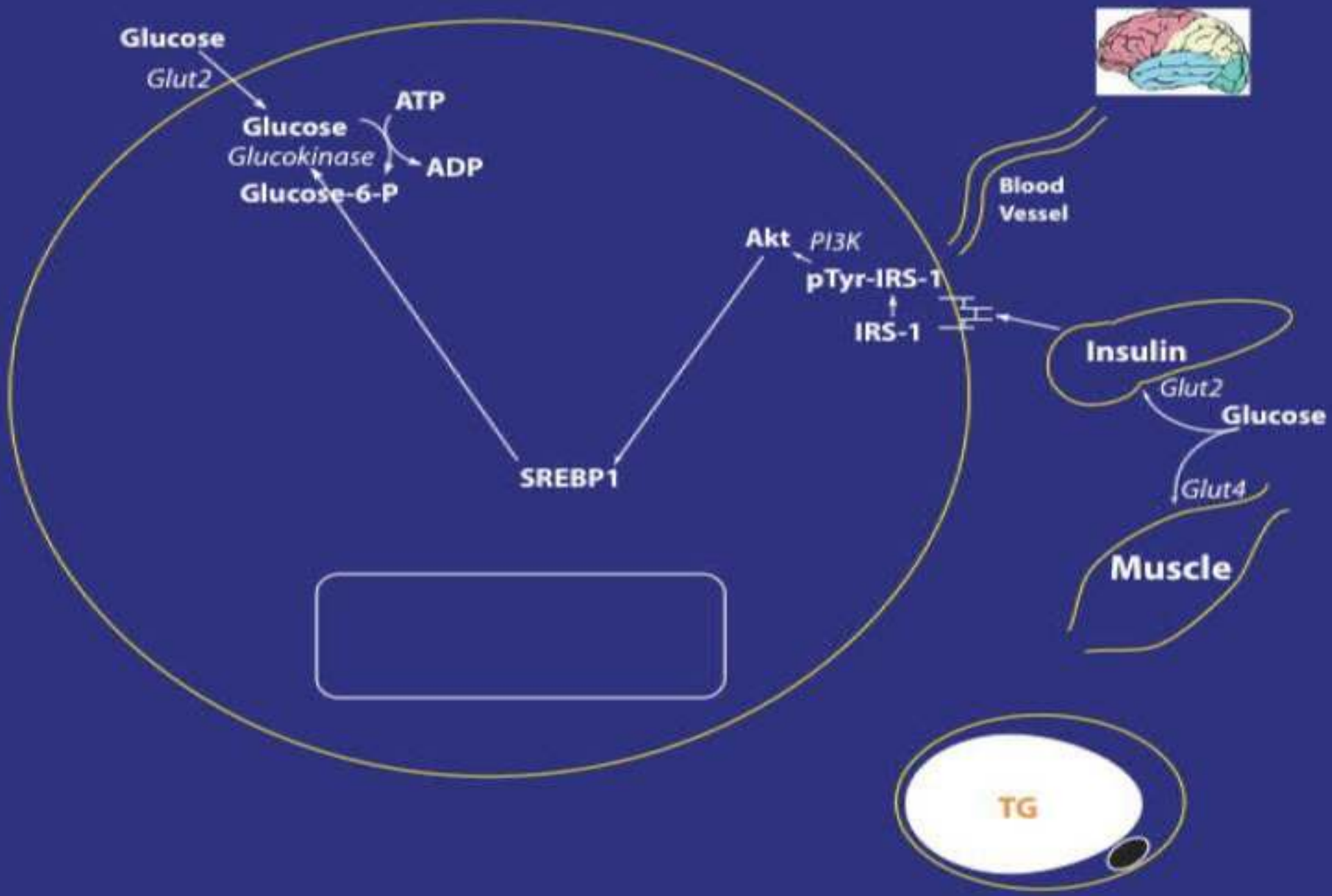
Metabolism of Glucose



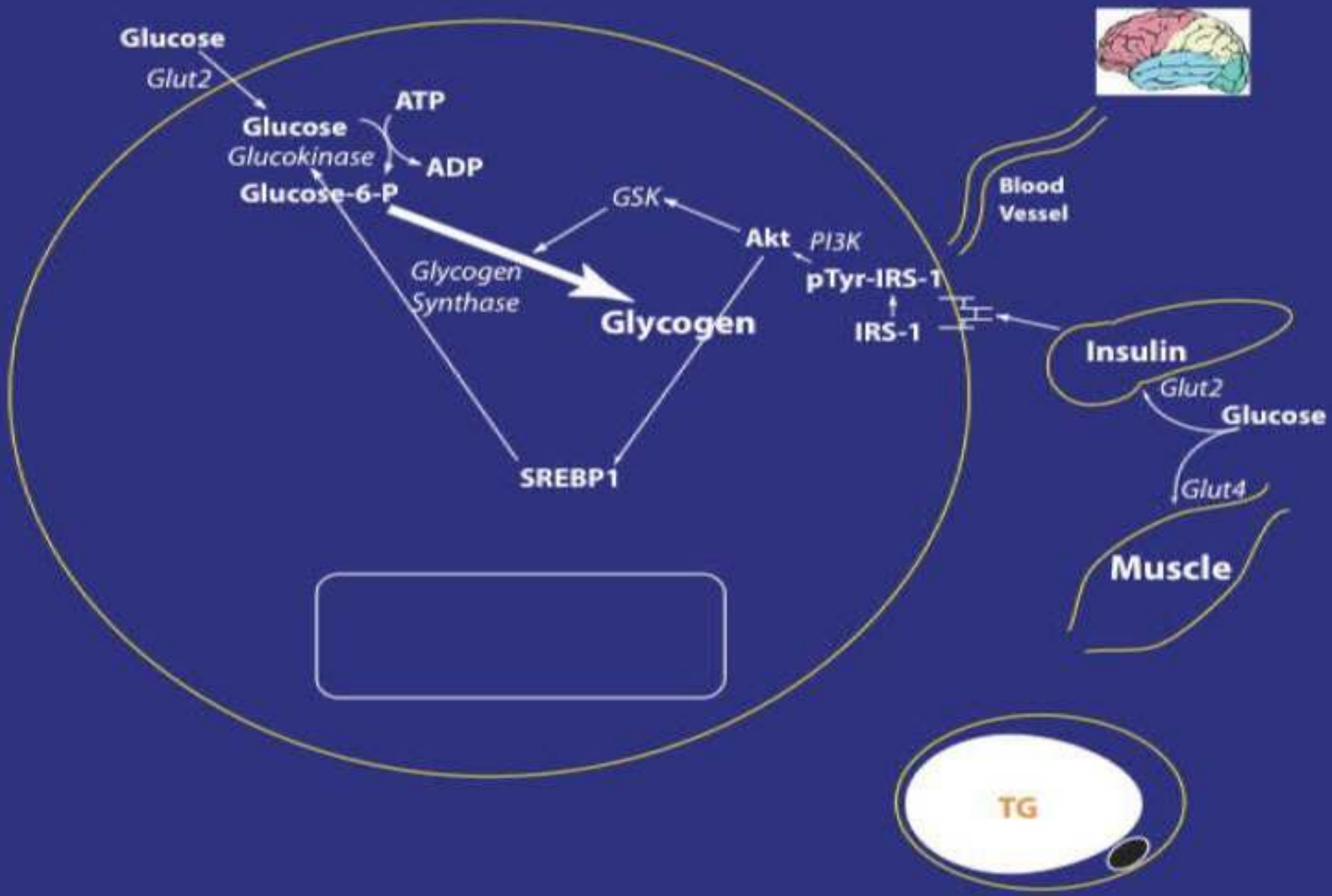
Metabolism of Glucose



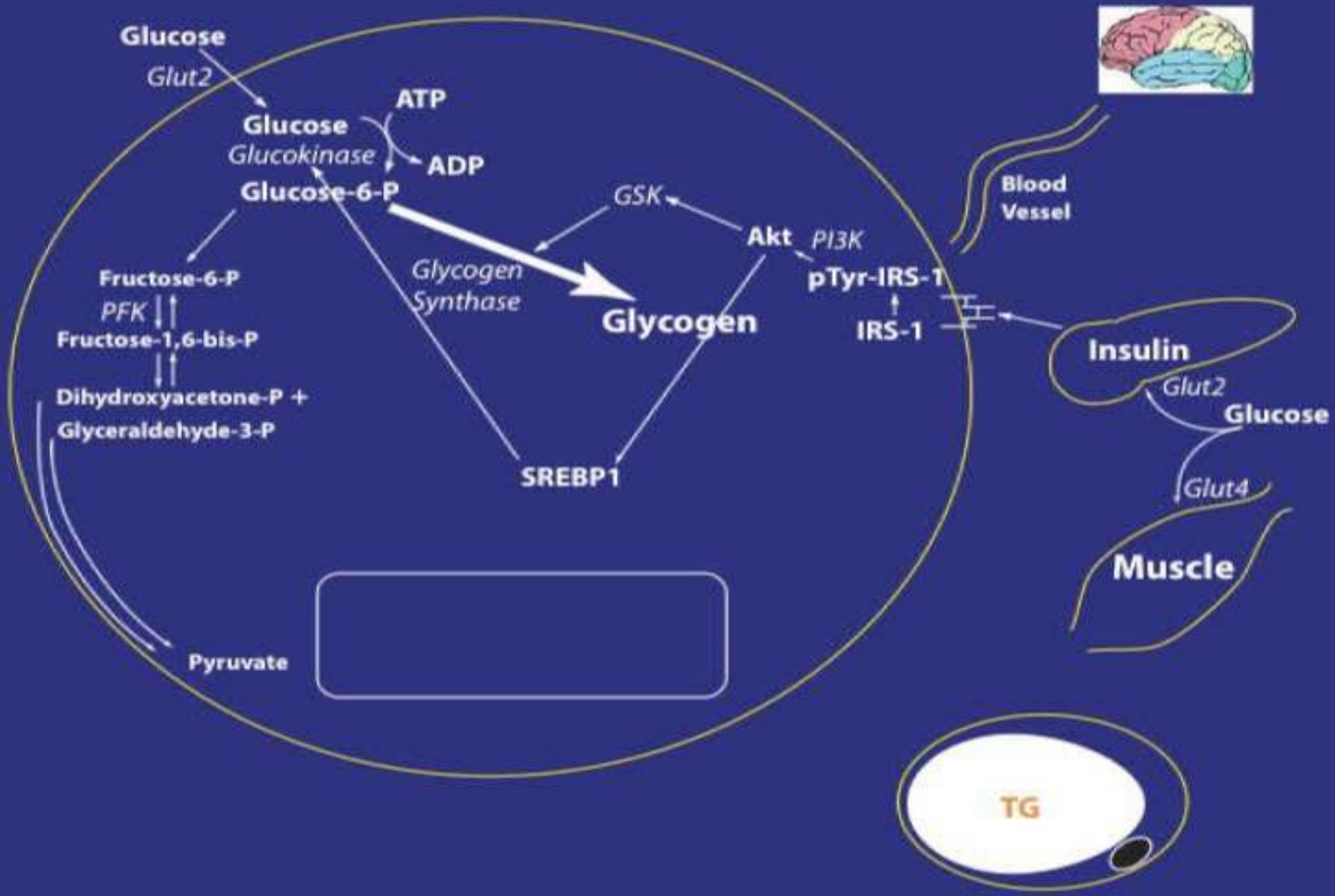
Metabolism of Glucose



Metabolism of Glucose



Metabolism of Glucose



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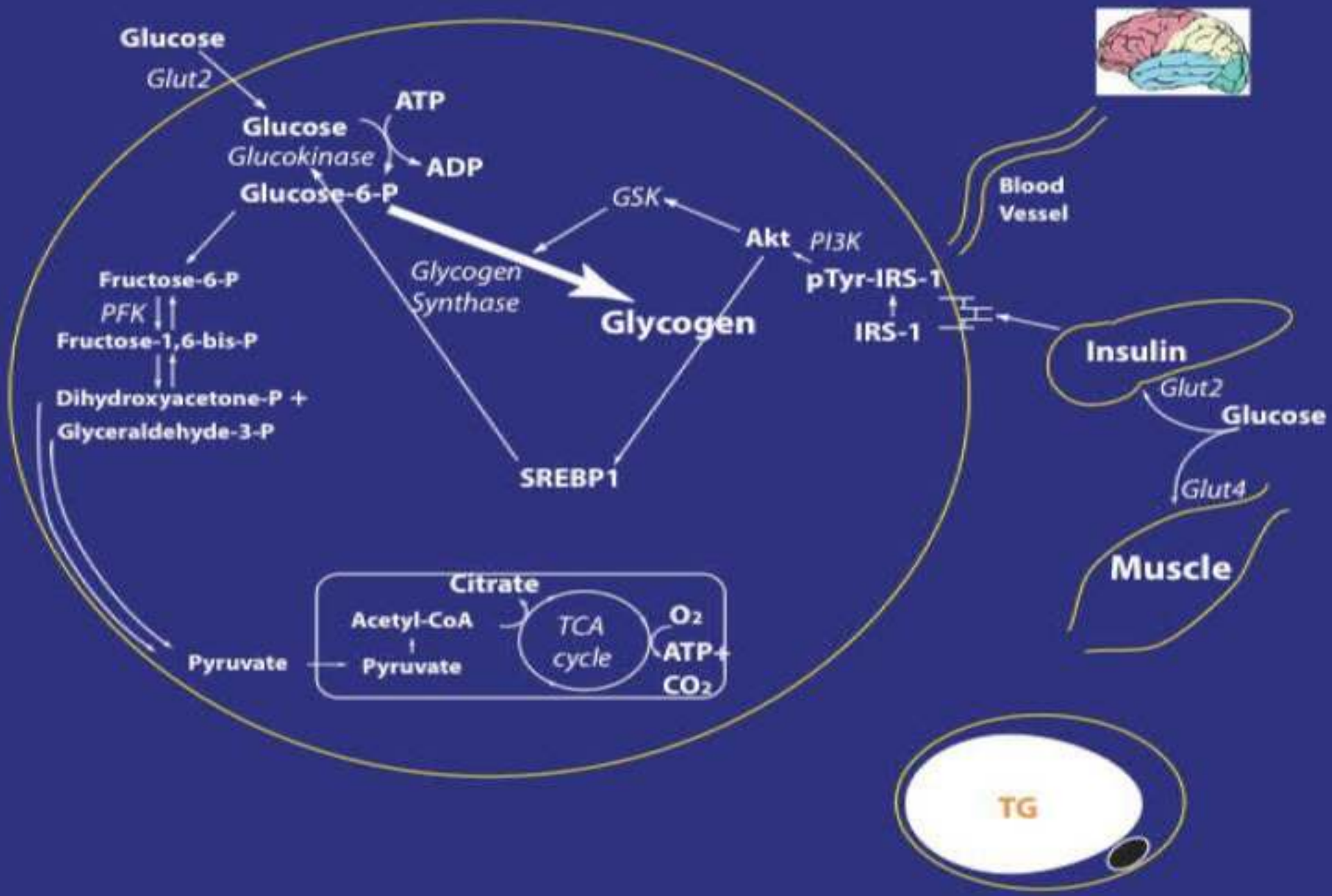
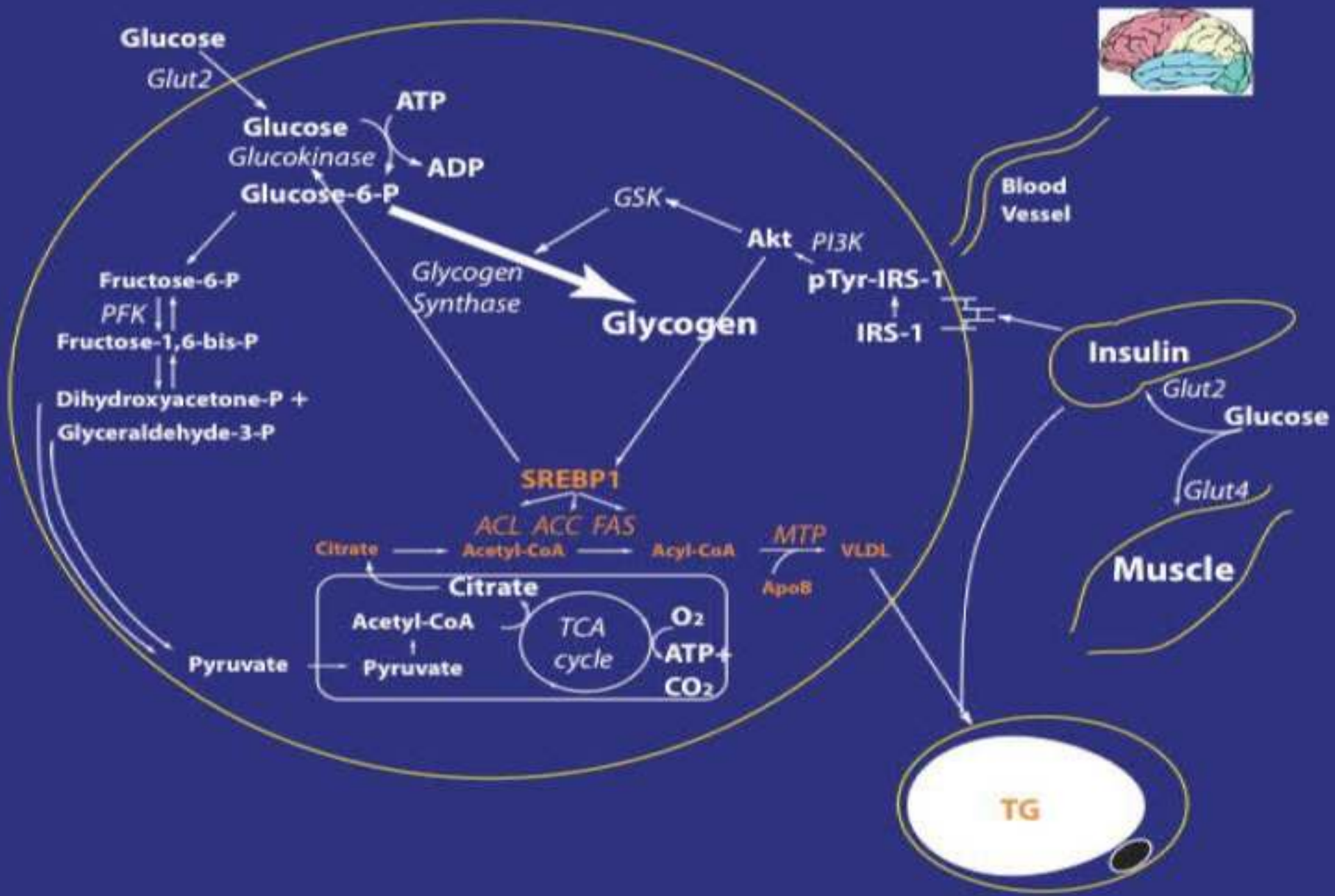
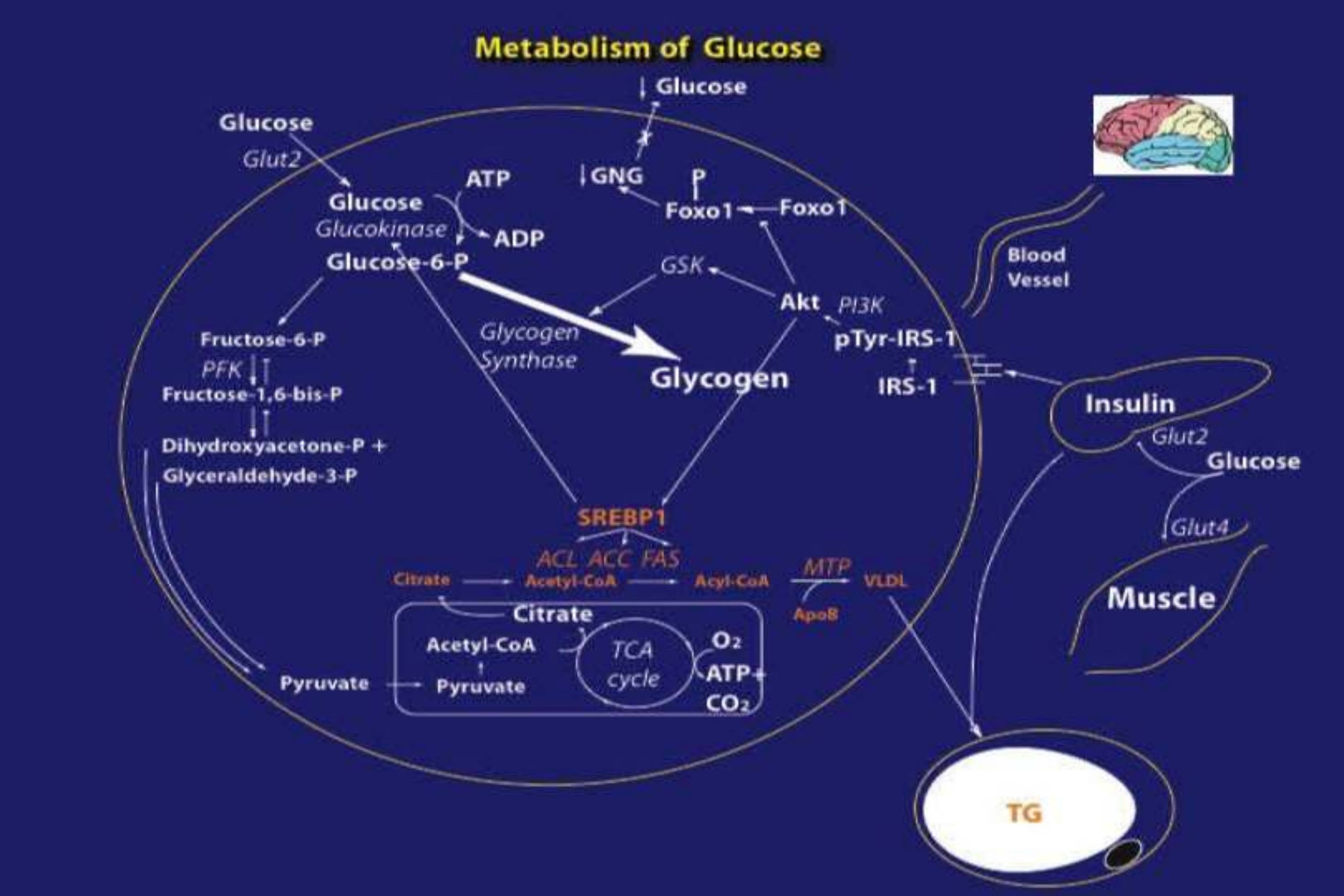
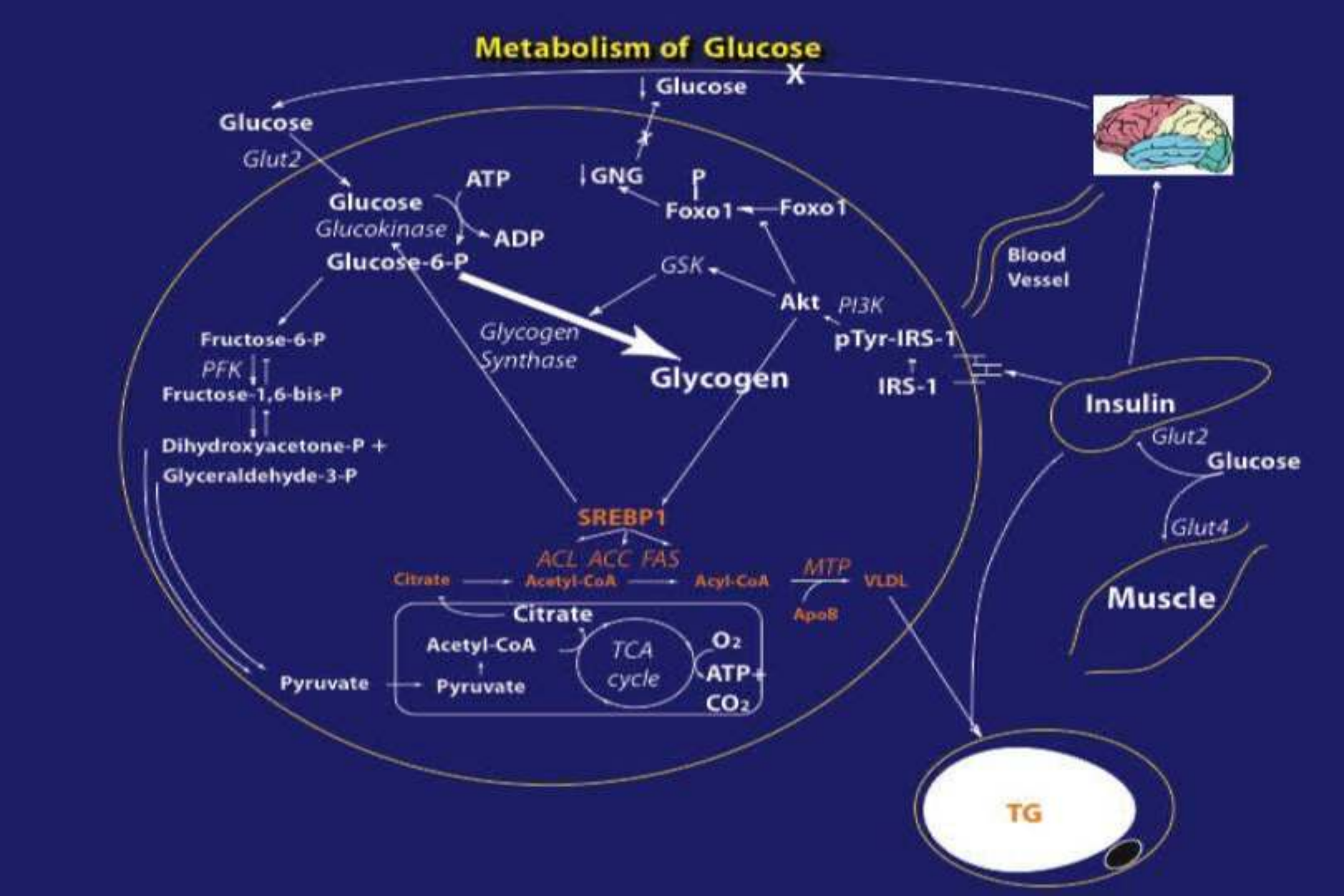


Metabolism of Glucose




Metabolism of Glucose
Glucose
Glucose
Glut2
ATP
GNG
P
Glucose
Glucokinase
ADP
Foxo1
Foxo1
Glucose-6-P
GSK
Akt
PI3K
Blood
Vessel
Fructose-6-P
PFK
Glycogen
Synthase
Glycogen
pTyr-IRS-1
IRS-1
Fructose-1,6-bis-P
Insulin
Glut2
Glucose
Dihydroxyacetone-P +
Glyceraldehyde-3-P
SREBP1
Glut4
ACL ACC FAS
MTP
Citrate
Acetyl-CoA
Acyl-CoA
VLDL
Muscle
Citrate
Apo8
Acetyl-CoA
TCA
cycle
O2
ATP
CO2
Pyruvate
Pyruvate
TG


Metabolism of Glucose
Glucose
X
Glucose
Glut2
Glucose
Glucokinase
ATP
ADP
Glucose-6-P
GNG
P
Foxo1
Foxo1
GSK
Akt
PI3K
pTyr-IRS-1
IRS-1
Glycogen Synthase
Glycogen
Fructose-6-P
PFK
Fructose-1,6-bis-P
Dihydroxyacetone-P +
Glyceraldehyde-3-P
SREBP1
ACL ACC FAS
Citrate
Acetyl-CoA
Acyl-CoA
MTP
VLDL
Apo8
Citrate
Acetyl-CoA
Pyruvate
Pyruvate
TCA cycle
O2
ATP
CO2
Blood Vessel
Insulin
Glut2
Glucose
Glut4
Muscle
TG

Detrimental Effects of Fructose

60 kcal
(+ 12 kcal
glucose)

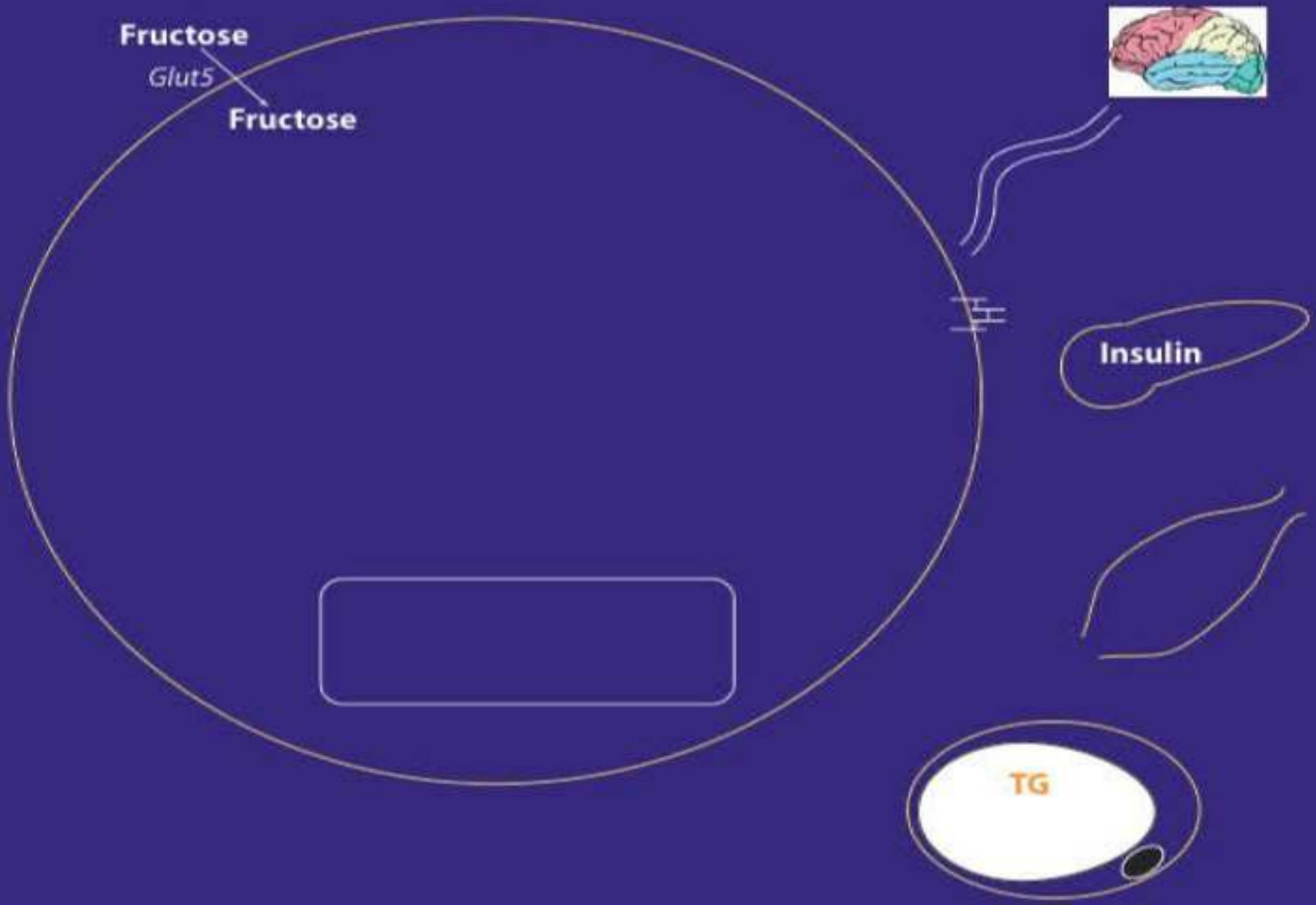
Fructose
100%

Insulin

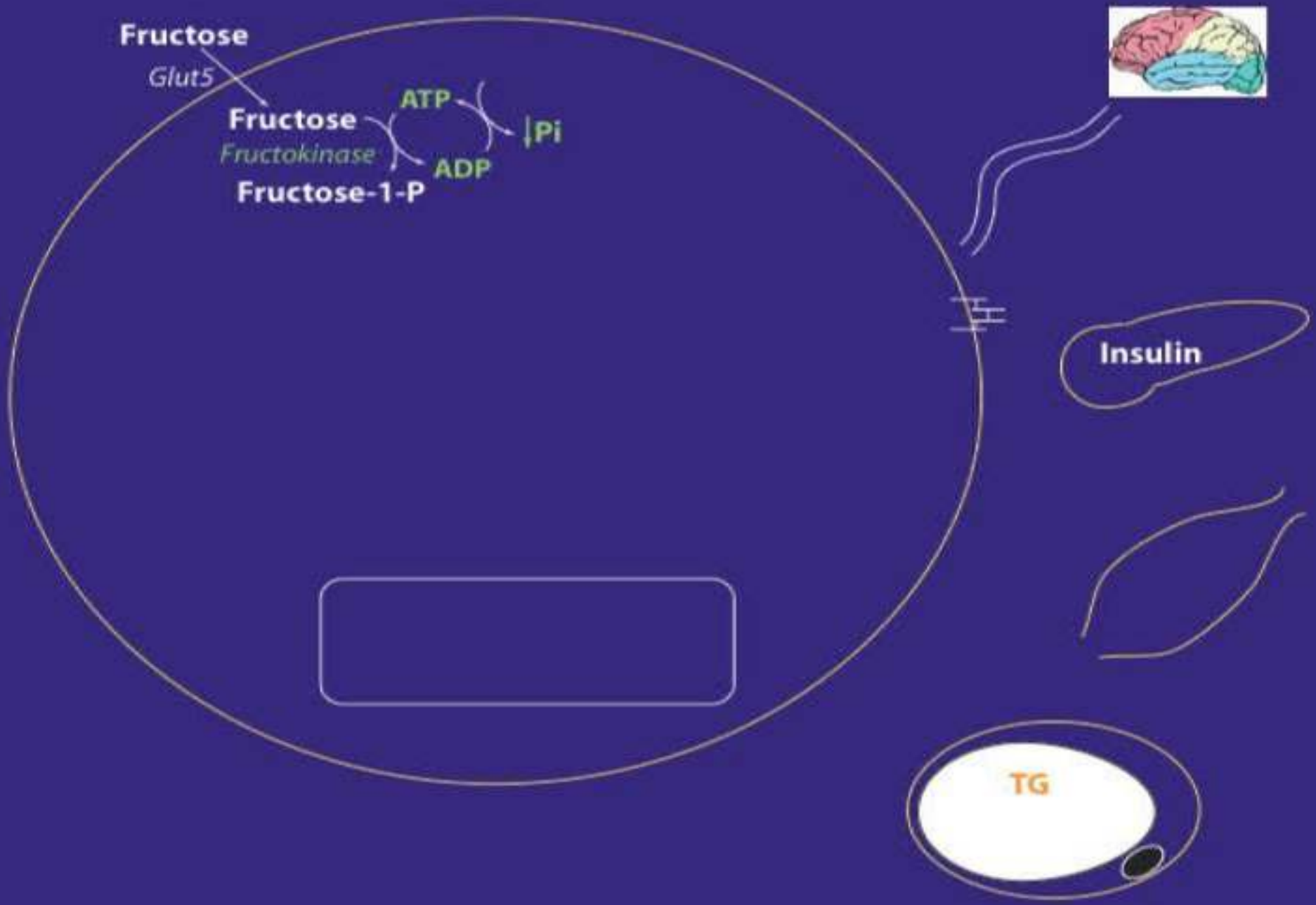
48 kcal

TG

Detrimental Effects of Fructose



Detrimental Effects of Fructose



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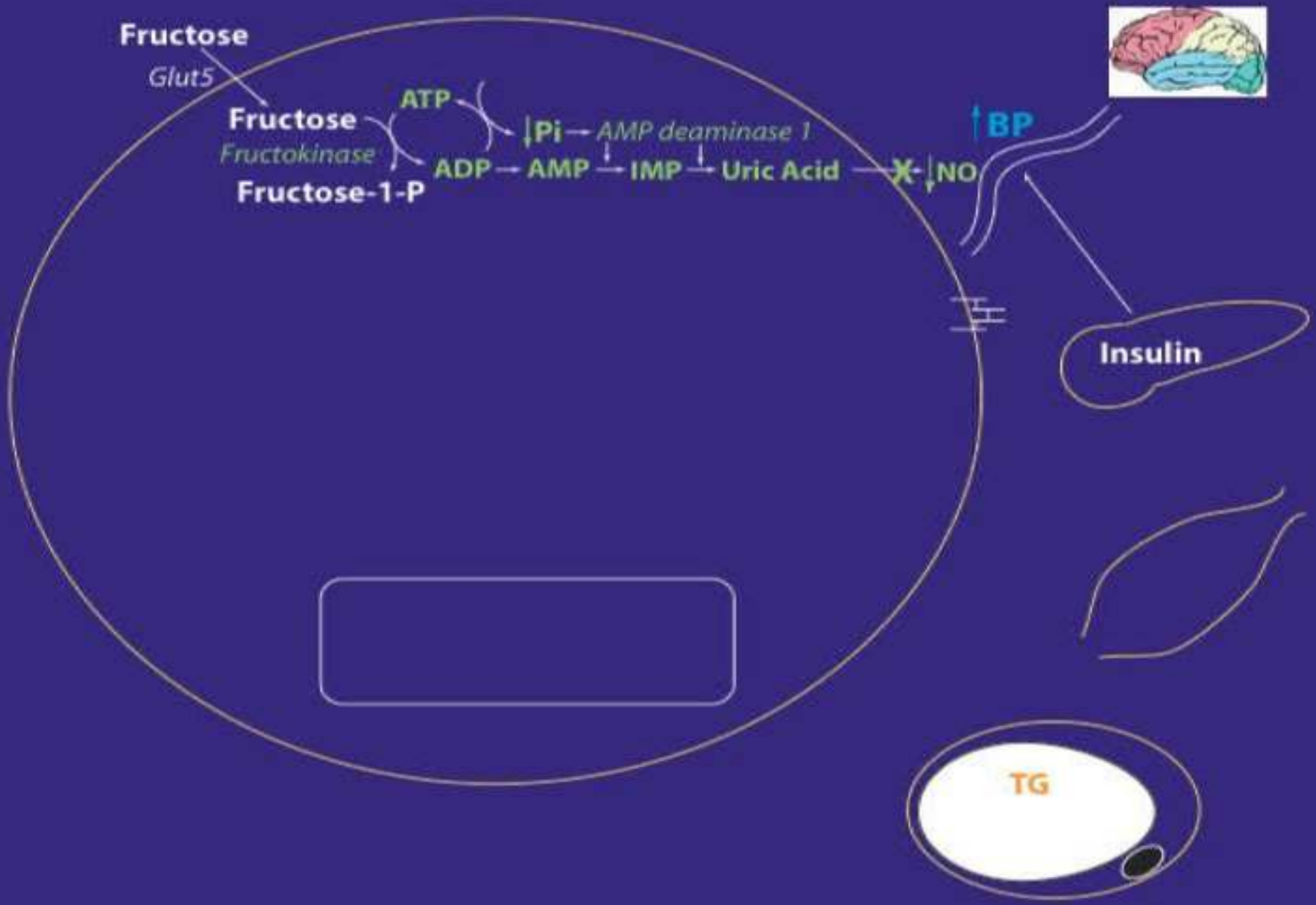

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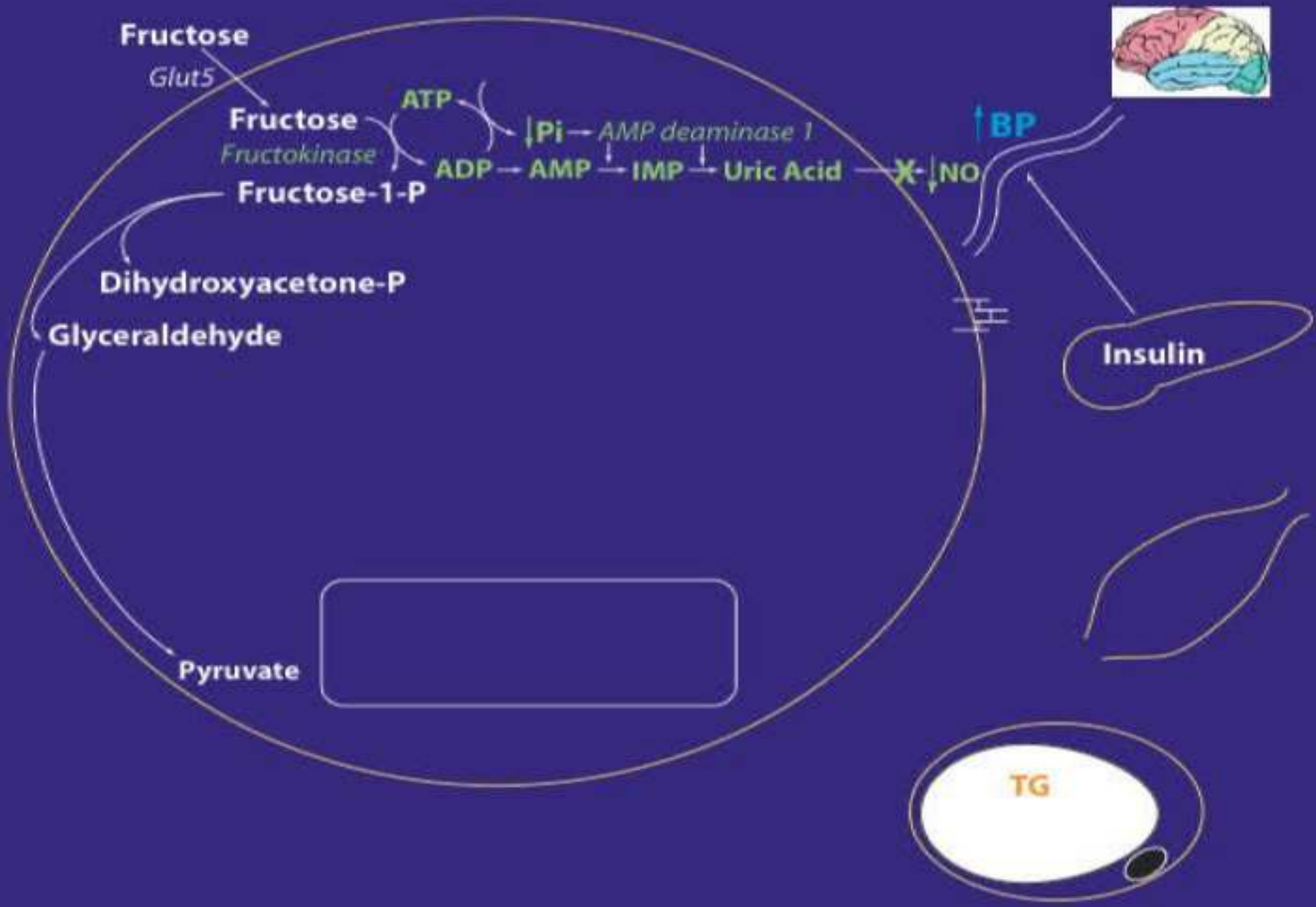

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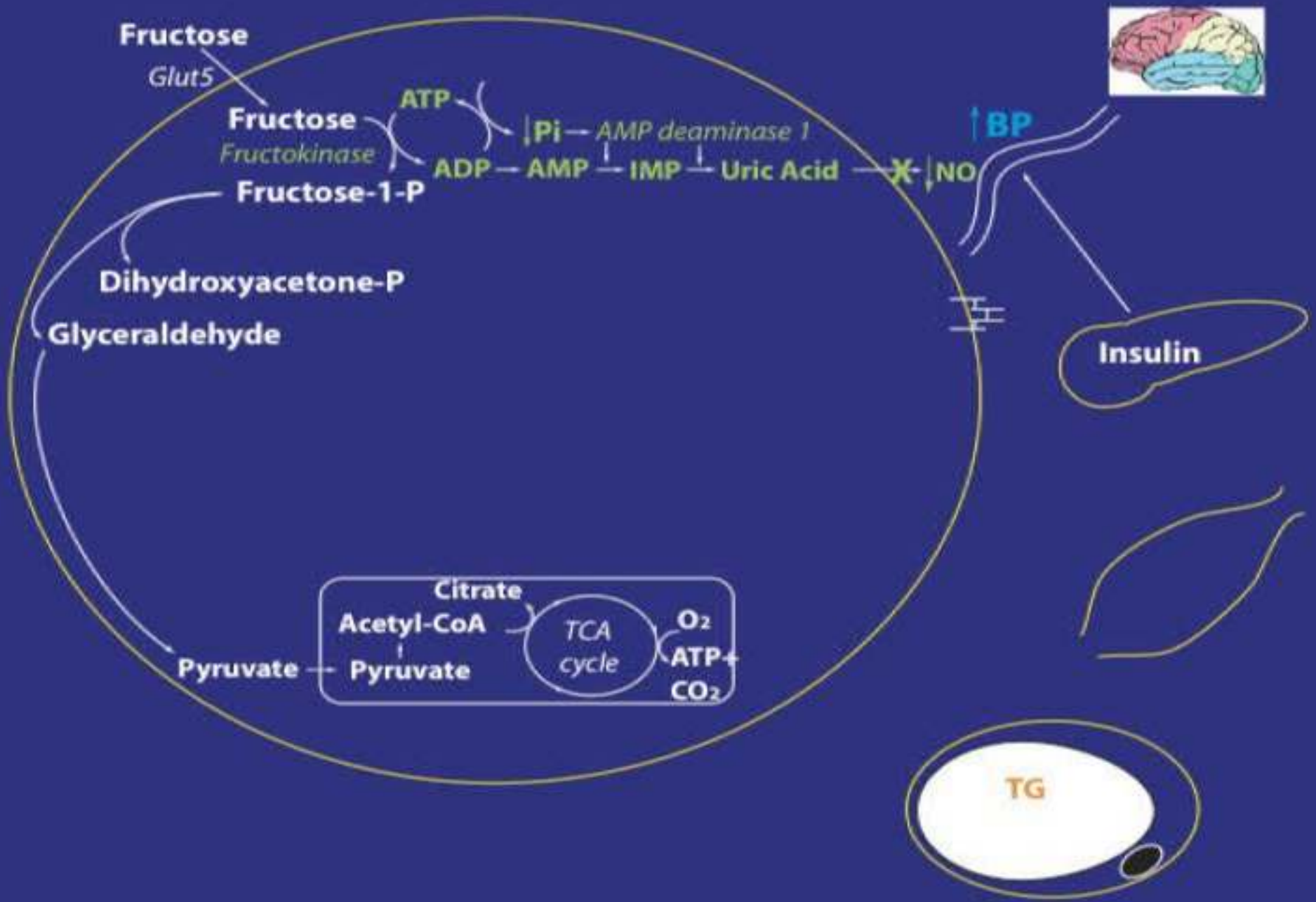
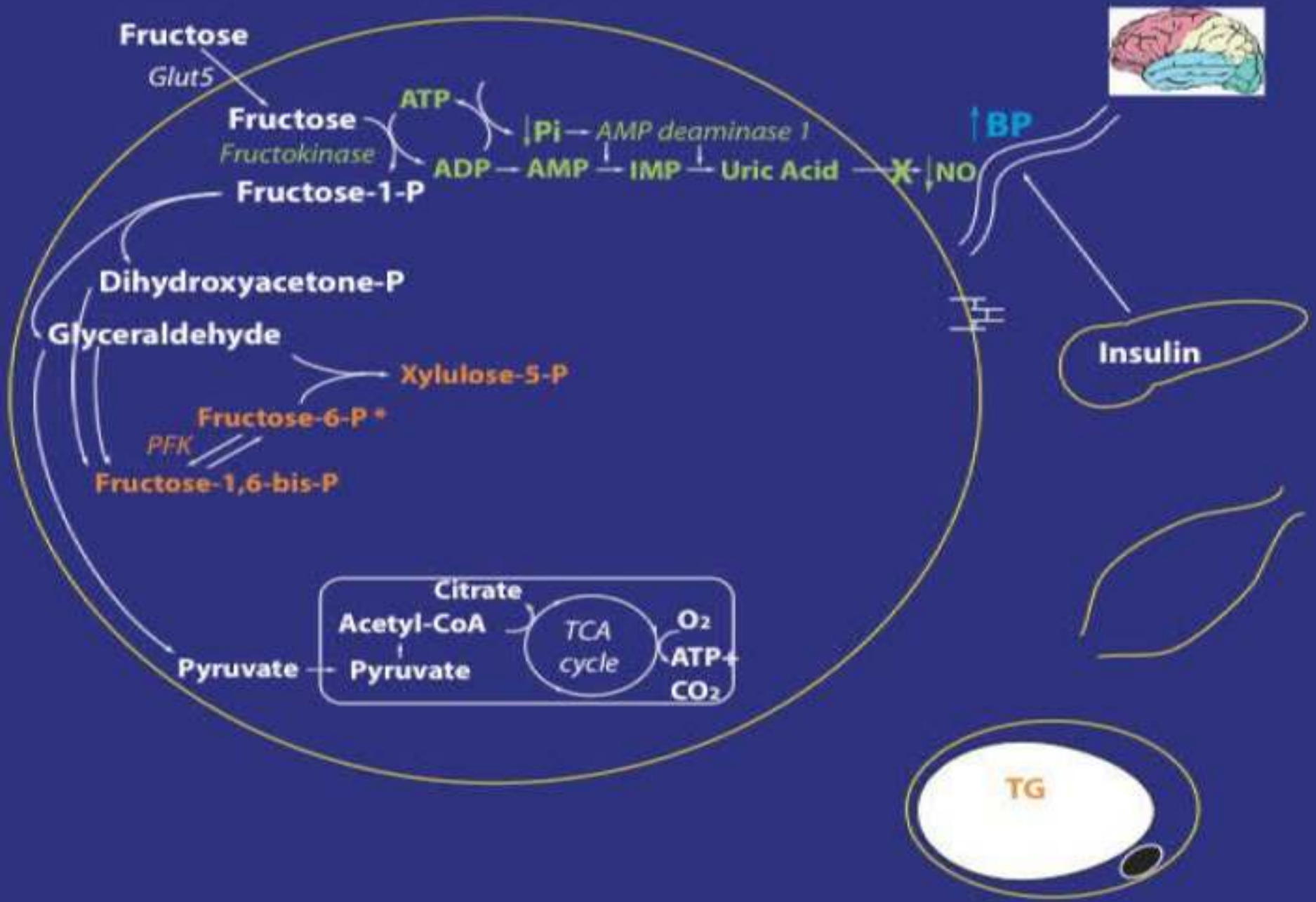


Detrimental Effects of Fructose



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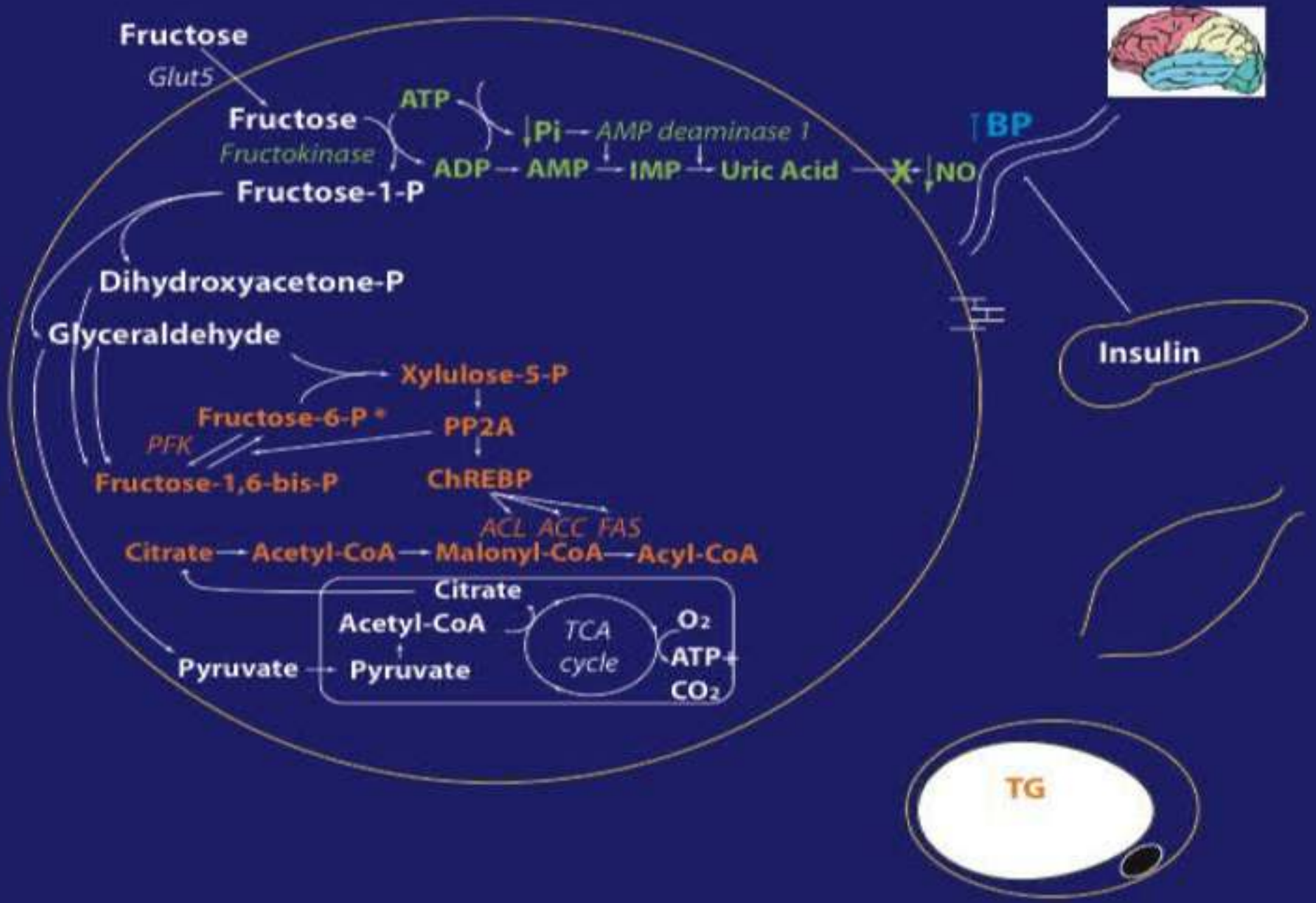
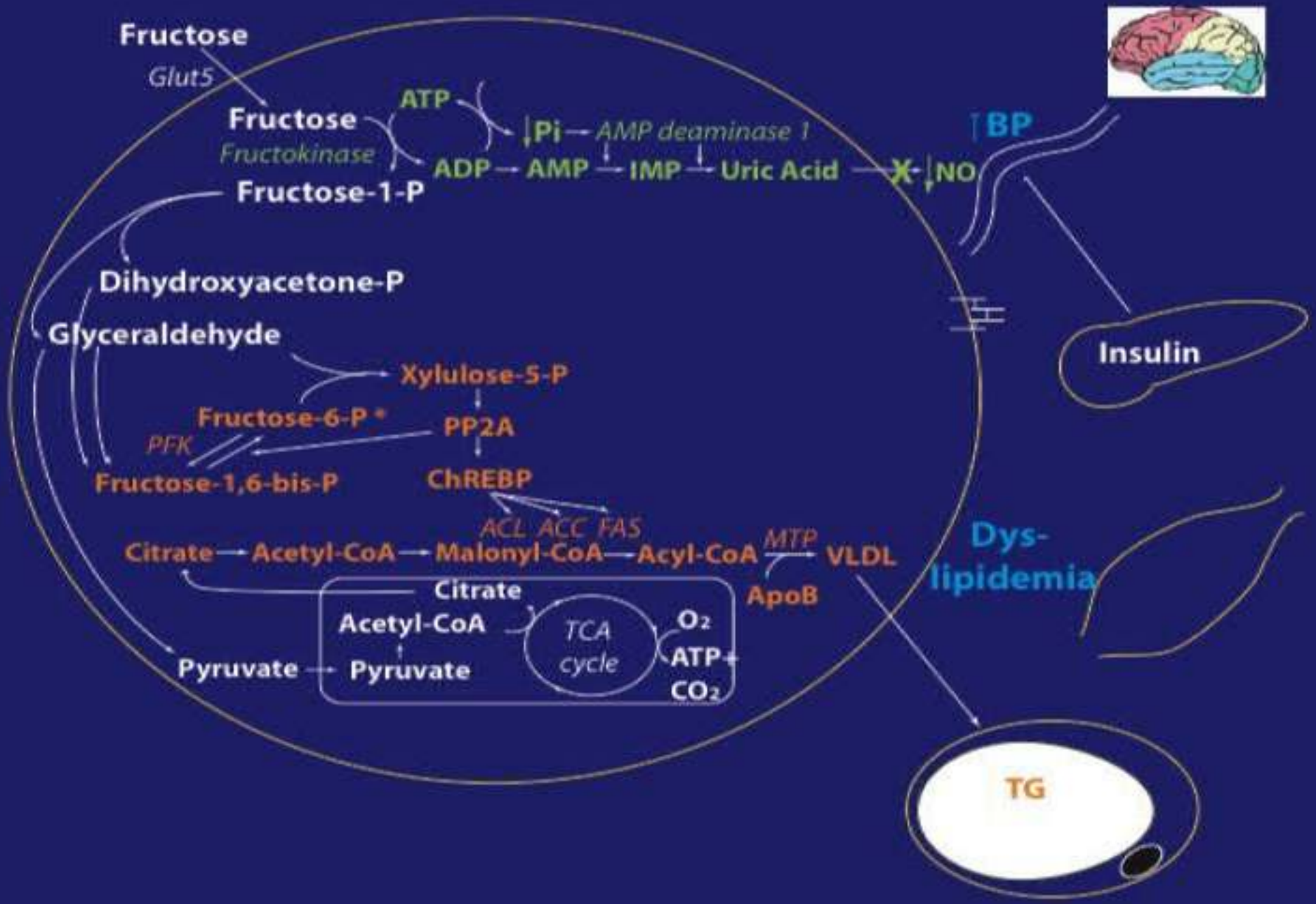


Detrimental Effects of Fructose



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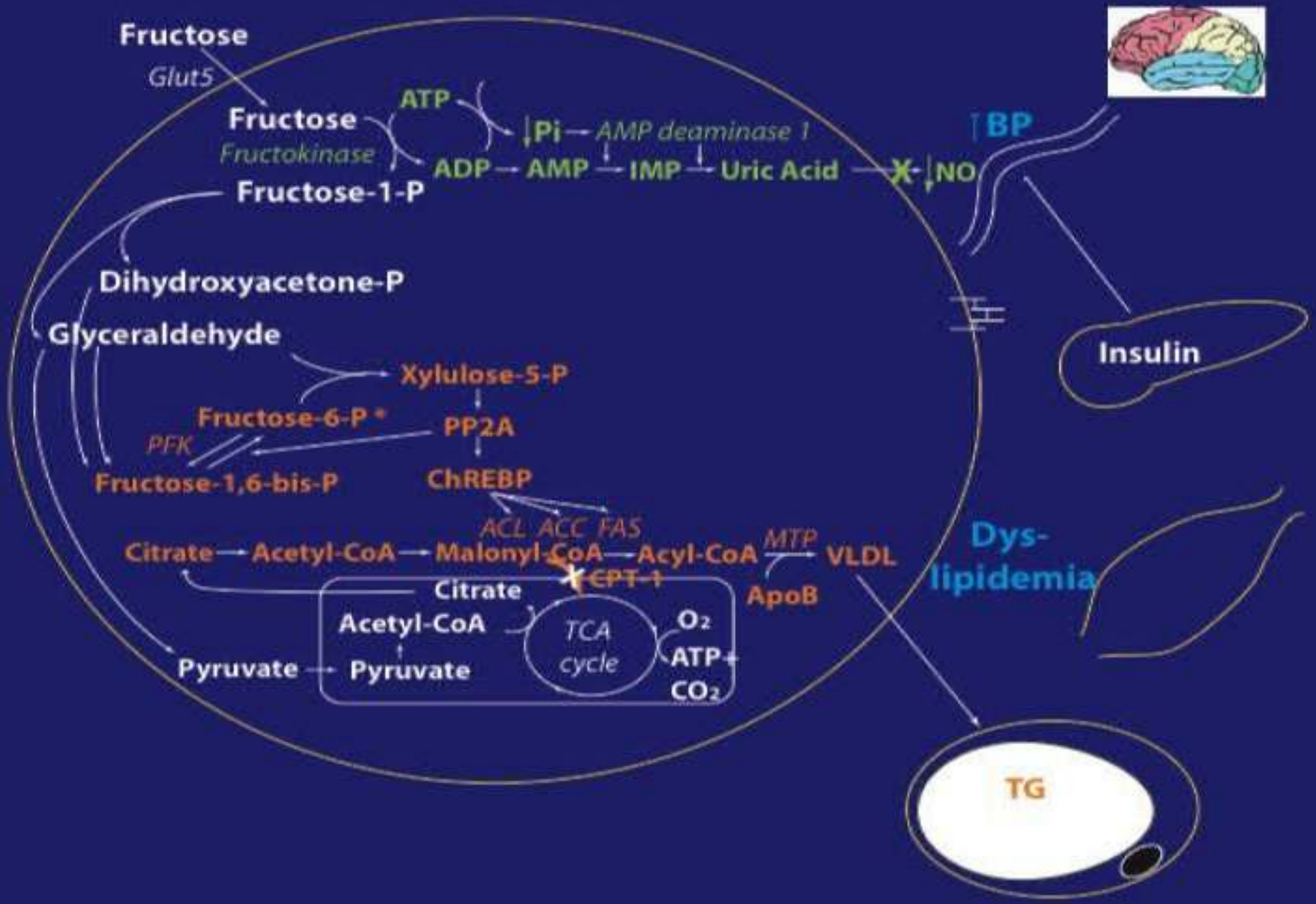

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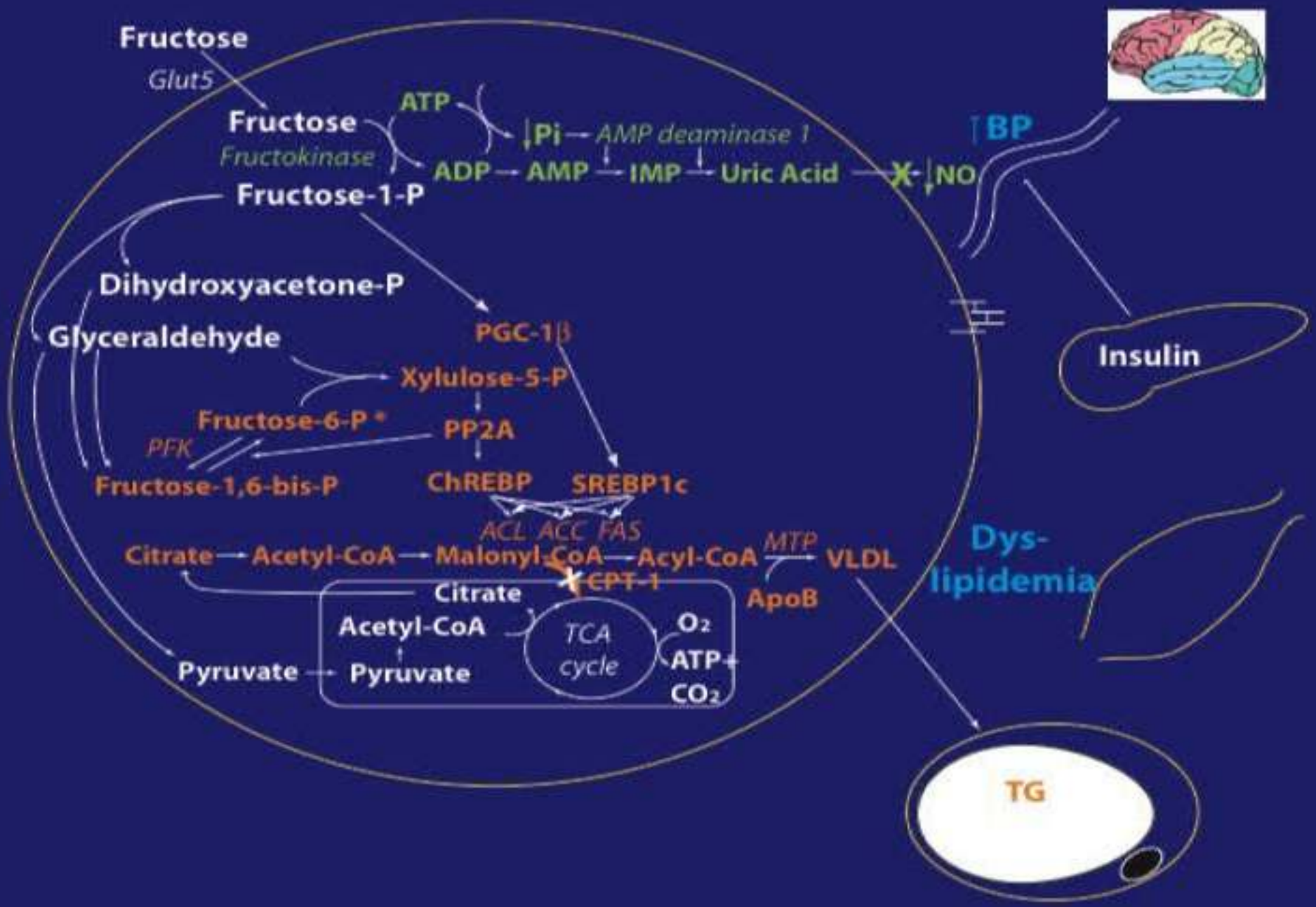

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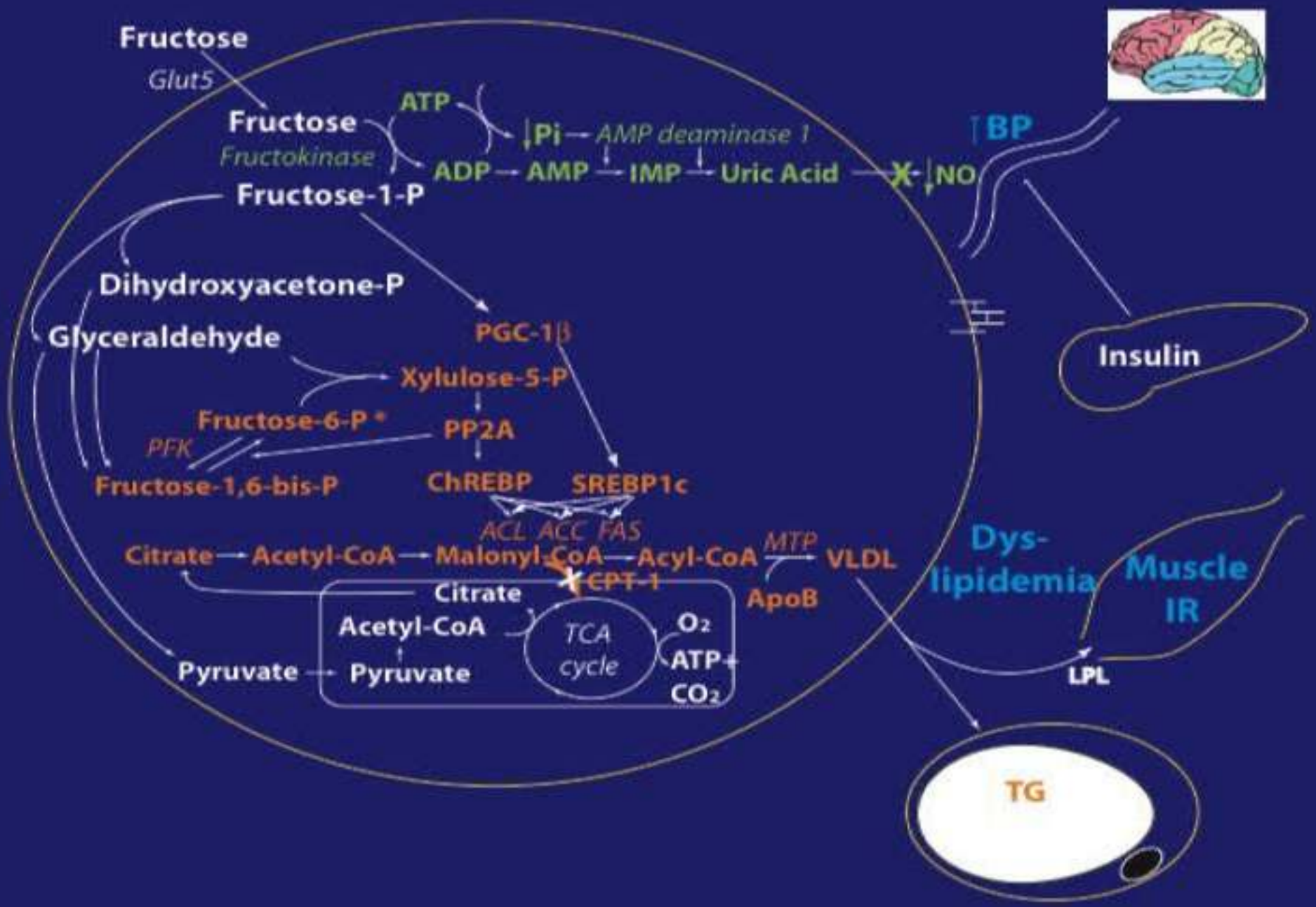

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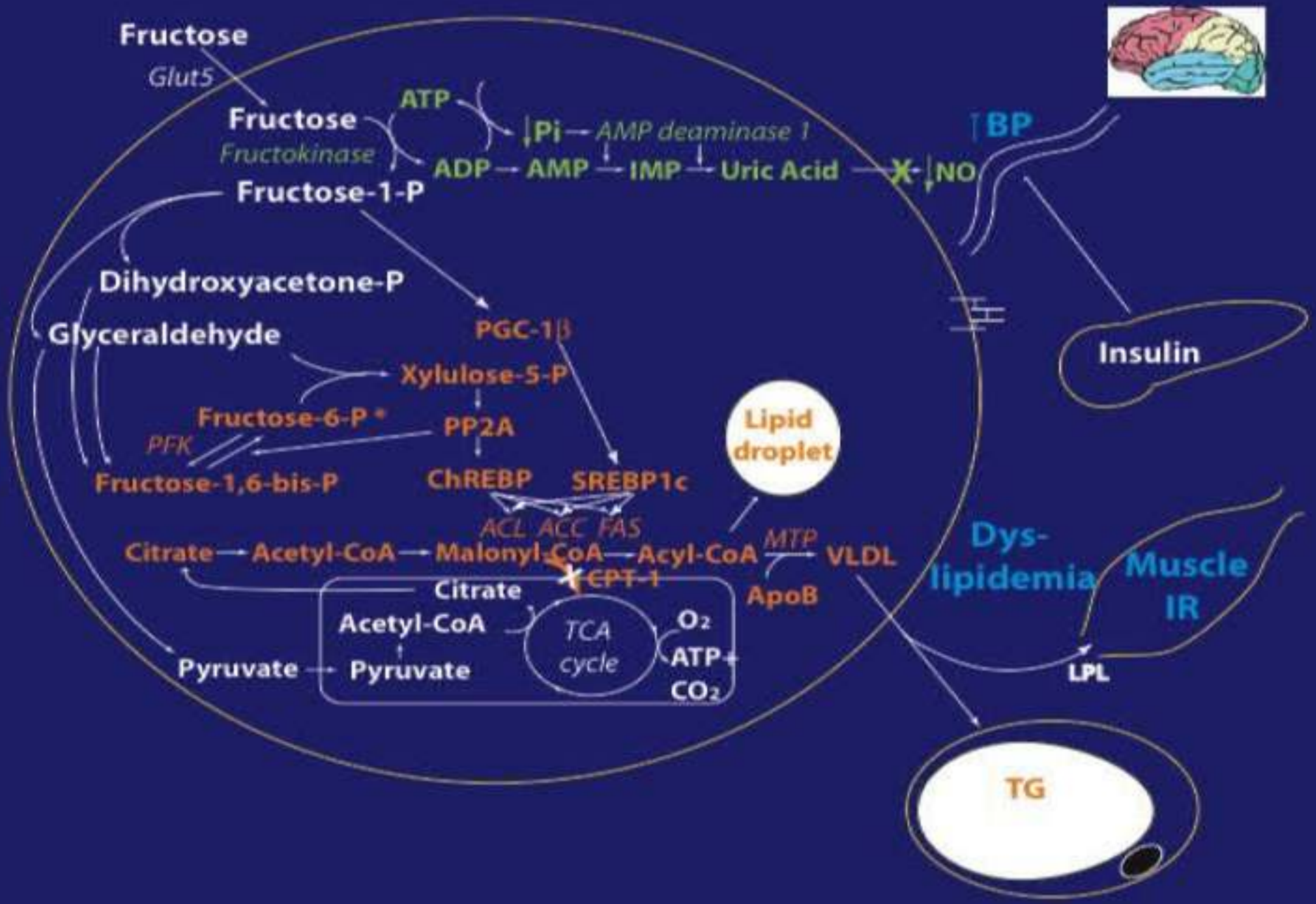

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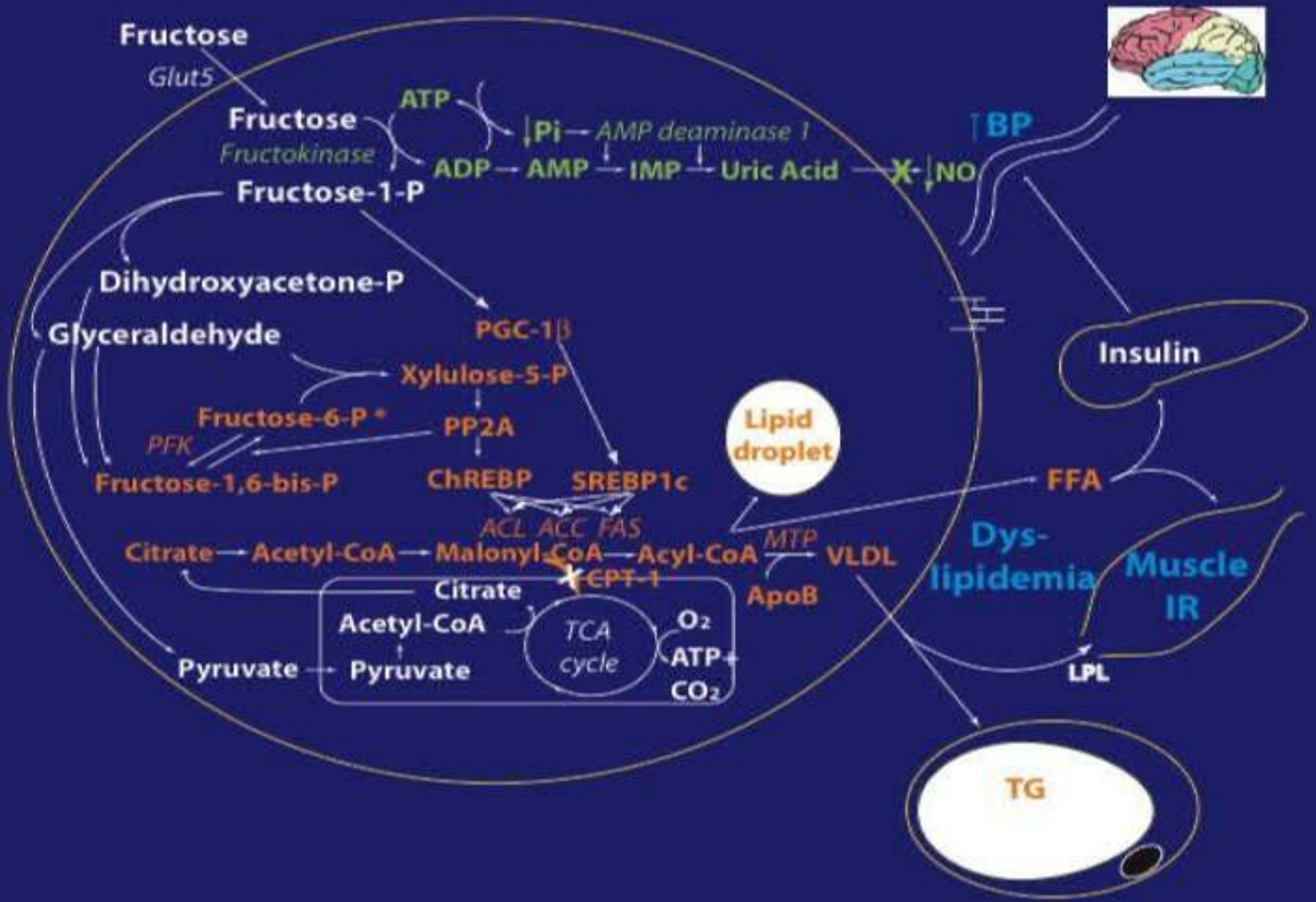

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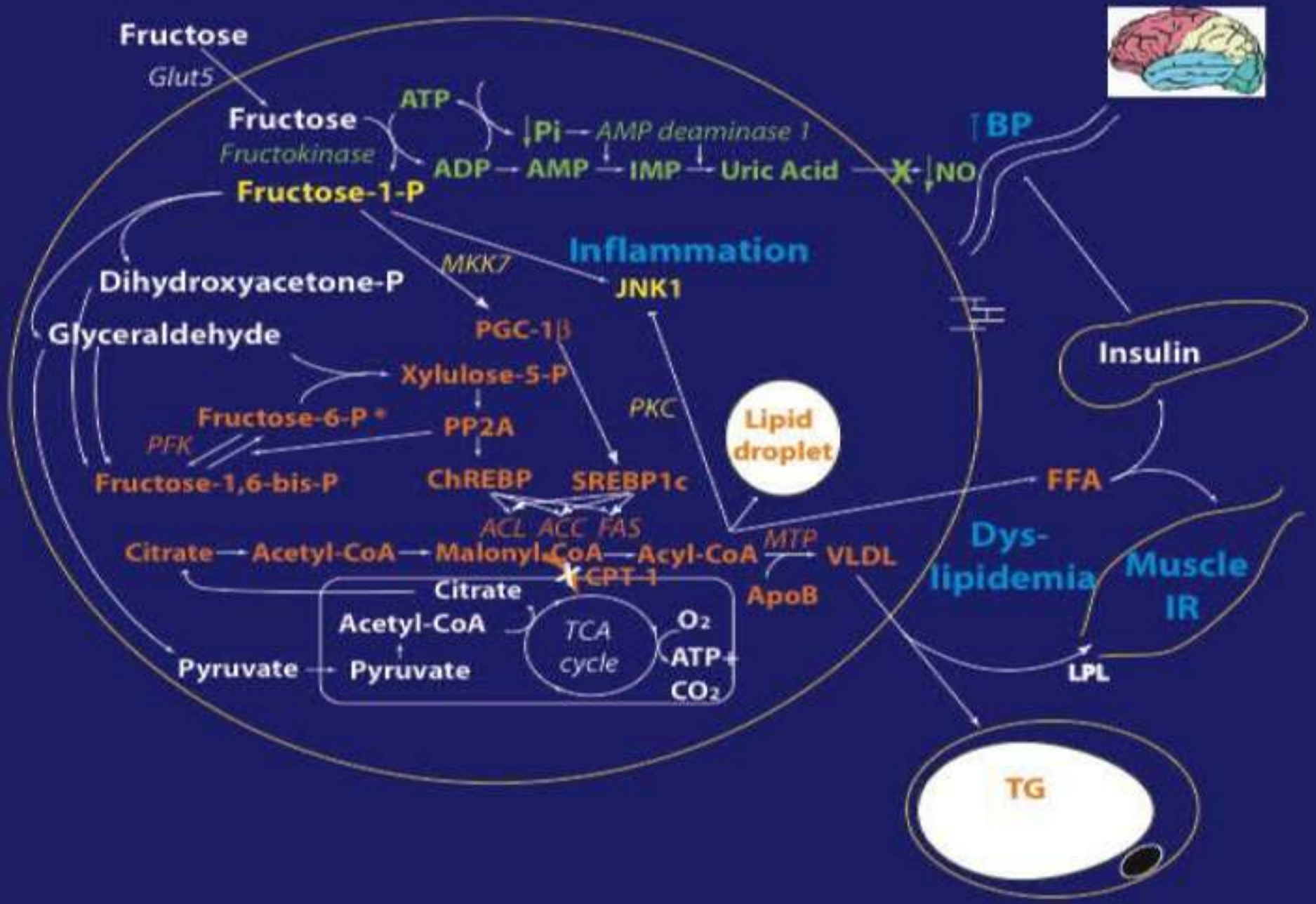
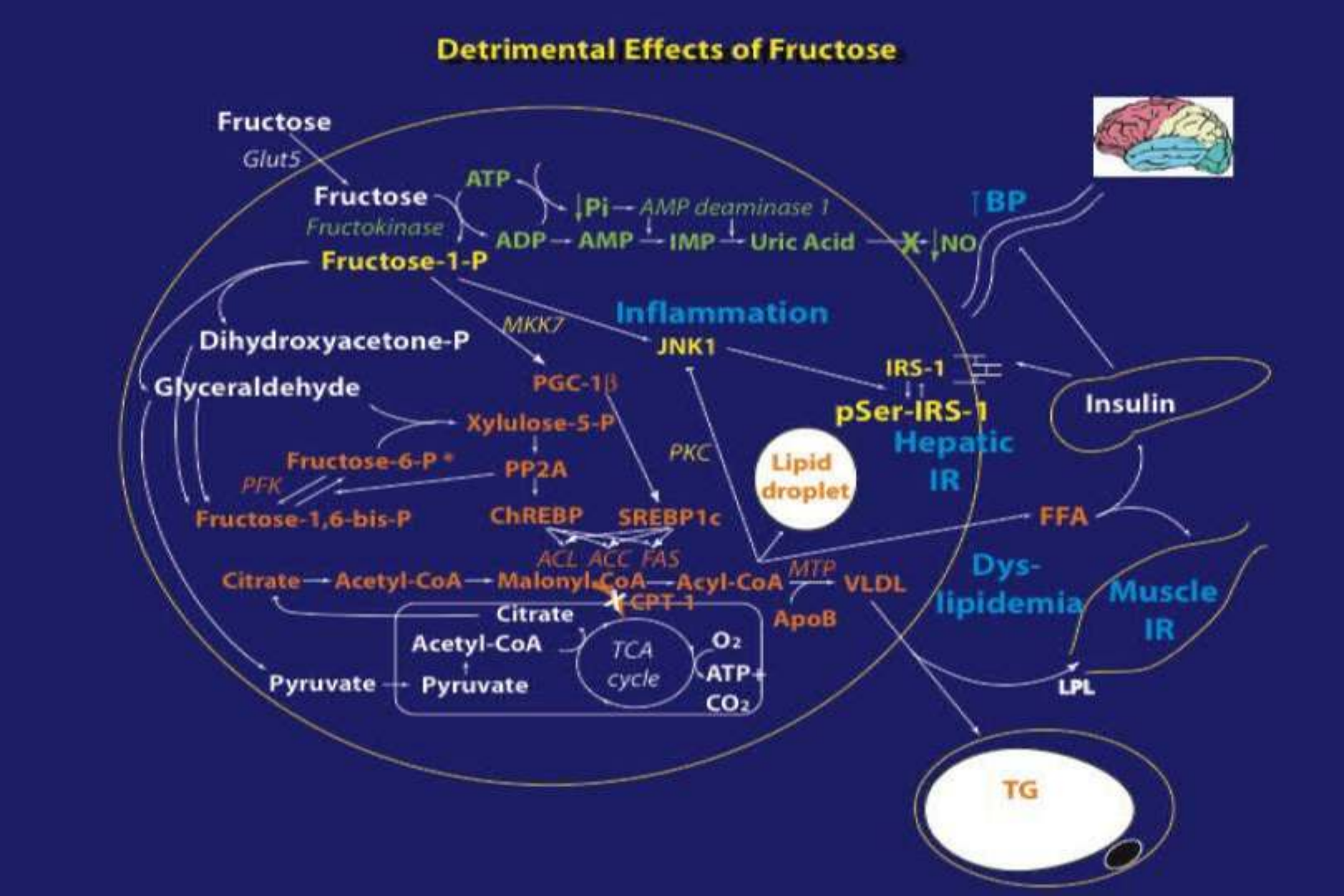
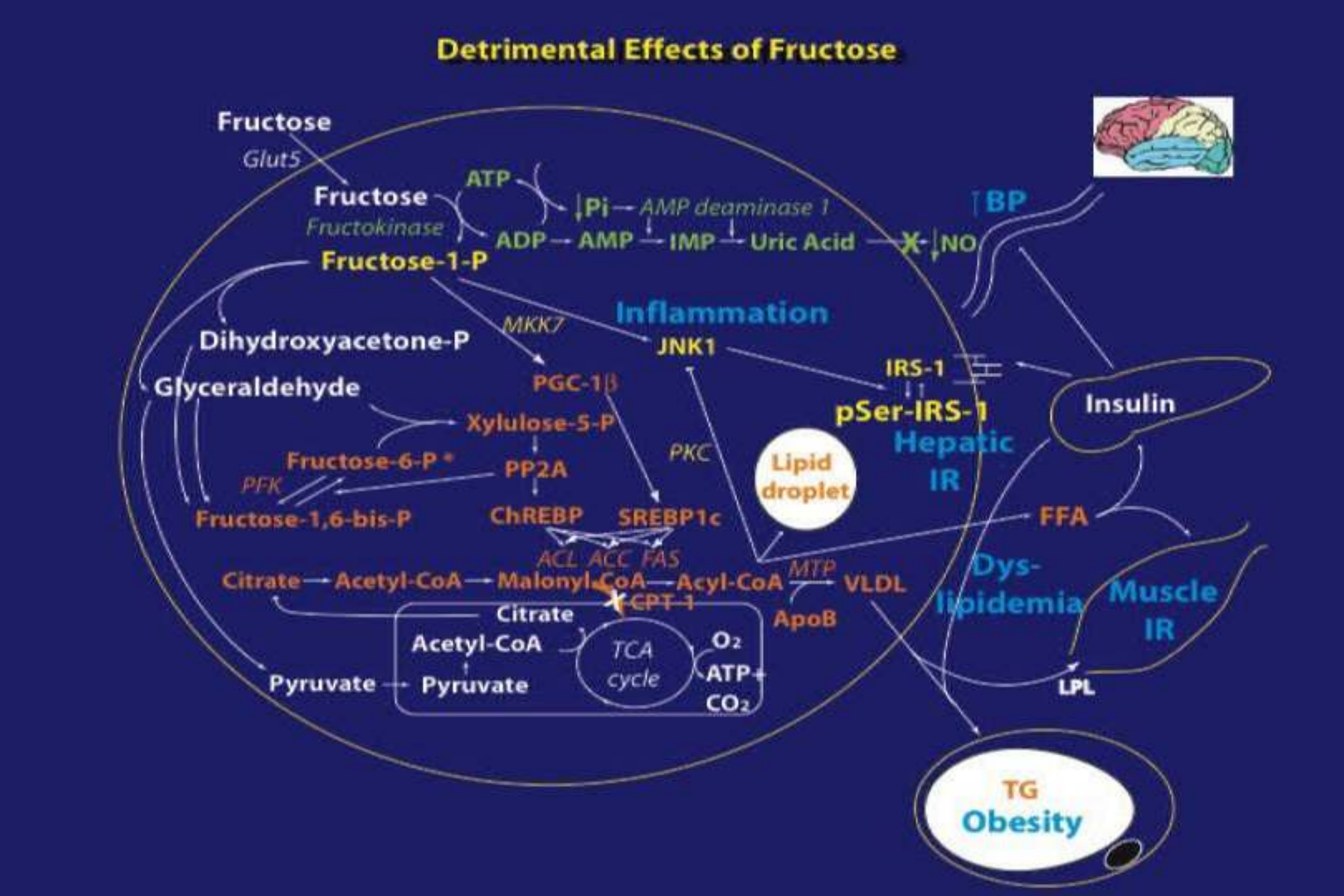



Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
Fructose-1-P
ATP
ADP
↓Pi
AMP deaminase 1
AMP
IMP
Uric Acid
X
↓NO
↑BP
Inflammation
MKK7
JNK1
Dihydroxyacetone-P
Glyceraldehyde
PGC-1β
Xylulose-5-P
Fructose-6-P
PP2A
PFK
Fructose-1,6-bis-P
PKC
ChREBP
SREBP1c
Lipid droplet
IRS-1
pSer-IRS-1
Hepatic IR
Insulin
FFA
ACL ACC FAS
Citrate
Acetyl-CoA
Malonyl-CoA
Acyl-CoA
CPT-1
MTP
VLDL
ApoB
Dys-lipidemia
Muscle IR
Citrate
Acetyl-CoA
TCA cycle
O2
ATP
CO2
Pyruvate
Pyruvate
LPL
TG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Fructose
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Fructose
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Fructose-1-P
ATP
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Pi
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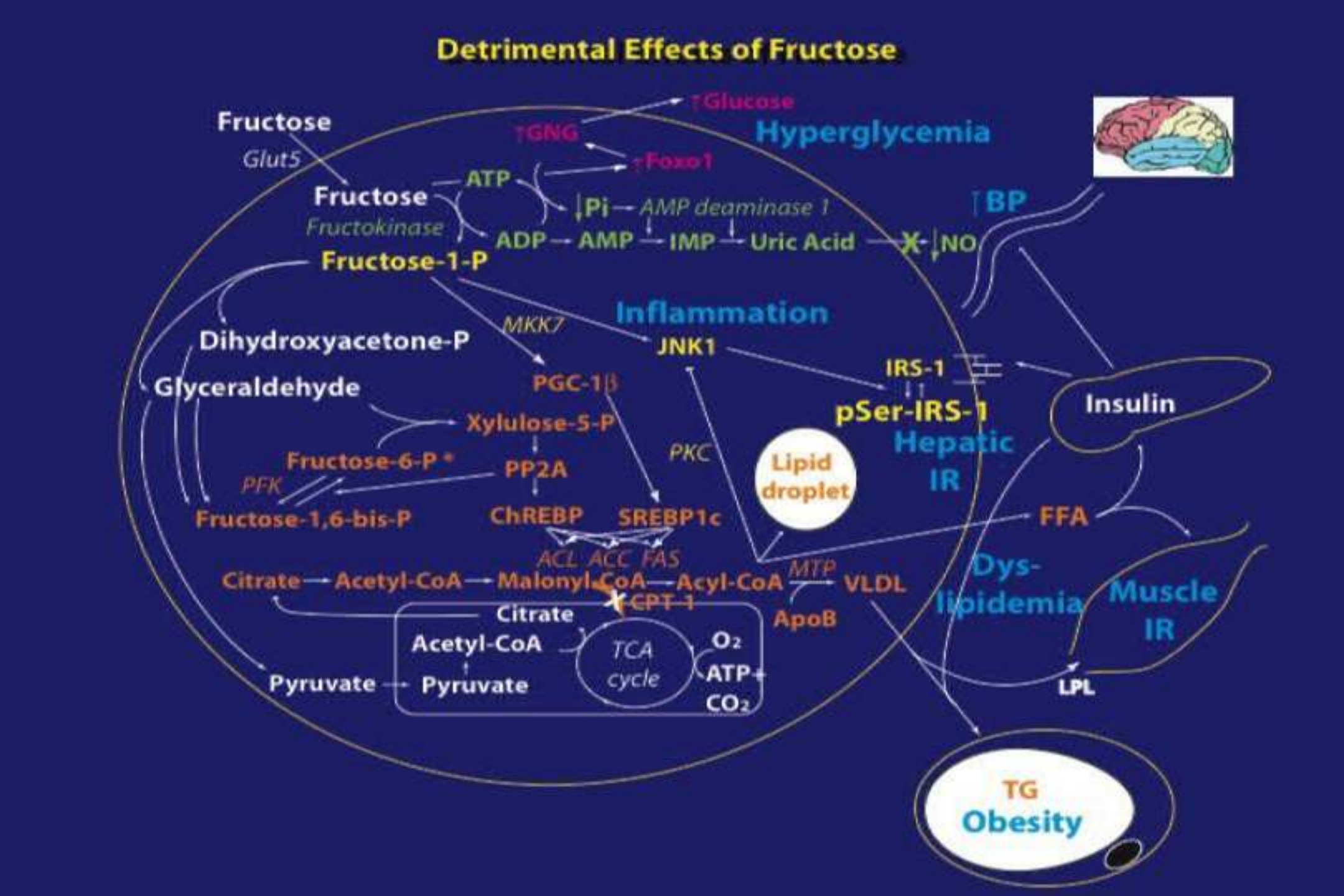
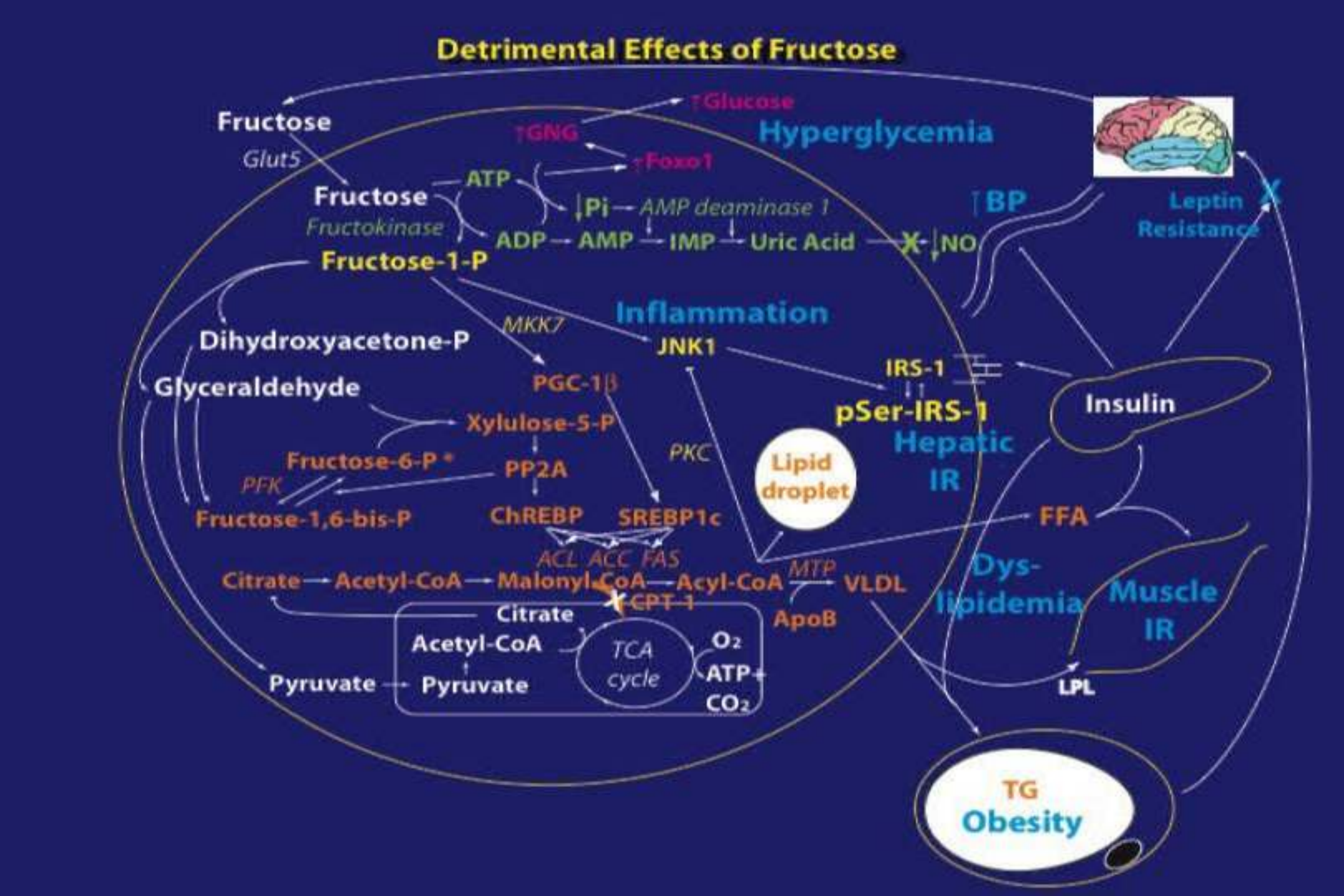
AMP
IMP
Uric Acid
X
NO
BP
Inflammation
MKK7
JNK1
Dihydroxyacetone-P
Glyceraldehyde
PGC-1β
Xylulose-5-P
PP2A
PKC
Fructose-6-P
PFK
Fructose-1,6-bis-P
ChREBP
SREBP1c
IRS-1
pSer-IRS-1
Hepatic IR
Insulin
Lipid droplet
FFA
ACL ACC FAS
Citrate
Acetyl-CoA
Malonyl-CoA
Acyl-CoA
CPT-1
MTP
VLDL
ApoB
Dys-lipidemia
Muscle IR
Citrate
Acetyl-CoA
TCA cycle
O2
ATP
CO2
Pyruvate
Pyruvate
LPL
TG
Obesity


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
Fructose-1-P
ATP
ADP
↓Pi
AMP deaminase 1
AMP
IMP
Uric Acid
↑GNG
↑Glucose
Hyperglycemia
↑Foxo1
↑BP
↓NO
Inflammation
MKK7
JNK1
Dihydroxyacetone-P
Glyceraldehyde
PGC-1β
Xylulose-5-P
Fructose-6-P
PP2A
PFK
Fructose-1,6-bis-P
PKC
ChREBP
SREBP1c
IRS-1
pSer-IRS-1
Hepatic IR
Insulin
Lipid droplet
FFA
ACL ACC FAS
Citrate
Acetyl-CoA
Malonyl-CoA
Acyl-CoA
CPT-1
MTP
VLDL
ApoB
Dys-lipidemia
Muscle IR
Citrate
Acetyl-CoA
Pyruvate
Pyruvate
TCA cycle
O2
ATP
CO2
LPL
TG
Obesity


Detrimental Effects of Fructose
Fructose
Glut5
Fructose
Fructokinase
Fructose-1-P
ATP
ADP
Pi
AMP deaminase 1
AMP
IMP
Uric Acid
NO
BP
Leptin Resistance
↑Glucose
↑GNG
↑Foxo1
Hyperglycemia
Inflammation
MKK7
JNK1
Dihydroxyacetone-P
Glyceraldehyde
PGC-1β
Xylulose-5-P
Fructose-6-P
PP2A
PFK
Fructose-1,6-bis-P
PKC
ChREBP
SREBP1c
IRS-1
pSer-IRS-1
Hepatic IR
Insulin
Lipid droplet
FFA
ACL ACC FAS
Citrate
Acetyl-CoA
Malonyl-CoA
Acyl-CoA
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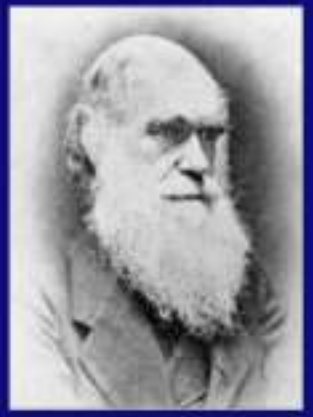
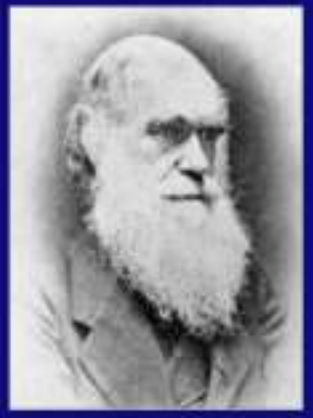


Fructose induces insulin resistance,
which induces leptin resistance

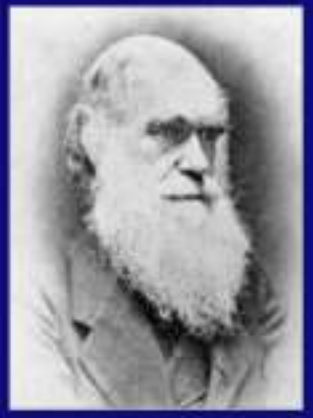


Fructose induces insulin resistance,
which induces leptin resistance

Does this make Darwinian sense?

Seasonal insulin resistance:

- Fructose was available at harvest, 1-2 months per year
- Followed by 4-5 months of winter, with no food available
- If leptin worked all the time, you couldn't store energy
- Selective advantage by inducing seasonal insulin resistance by gorging on fruit, while it was available



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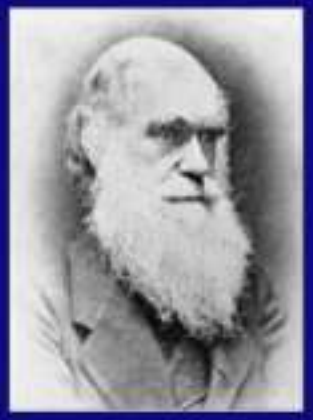
But fructose is now available globally 24/7/365,
and consumed in unlimited amounts
And unopposed by fiber (read: orange juice)

Summary: leptin and insulin resistance
The Darwinian explanation for the obesity epidemic



- Obesity means leptin resistance, or "brain starvation"
- The starvation response causes recidivism
- Energy expenditure and quality of life are the same thing
- Defects in insulin signaling promote leptin resistance
- Insulin appears to be an "endogenous leptin antagonist"
- Fructose, by driving *de novo* lipogenesis, induces hepatic insulin resistance, driving both weight gain and continued consumption
- Our environment is insulinogenic; we have to "get the insulin down"

Further reading

Fast Food, Central Nervous System Insulin Resistance, and Obesity

Elvira Isganaitis, Robert H. Lustig

Arterioscler Throm Vasc Biol 25:2451, 2005

Is fast food addictive?

Andrea K. Garber, Robert H. Lustig

Curr Drug Abuse Rev (in press, 2011)

The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome

Jung Sub Lim, Michele Mietus-Snyder, Annie Valente, Jean-Marc Schwarz and Robert H. Lustig

Nat Rev Gastroenterol Hepatol 7:251, 2010

eat right. American Dietetic Association

RESEARCH

Review

Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol

ROBERT H. LUSTIG, MD

J Am Diet Assoc 110:1305, 2010

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