Sweet Fructose with Sticky Consequences: A Look at IBS

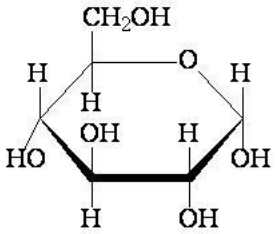
BRIANA RAPP

Topics to Cover

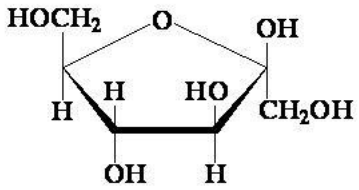
1. The digestion of fructose compared to glucose and galactose
2. The role of fructose in IBS/Journal article
3. Solutions/MNT for IBS and fructose malabsorption
4. What HFCS has to do with IBS and the general population

Digestion of Fructose Compared to Glucose and Galactose

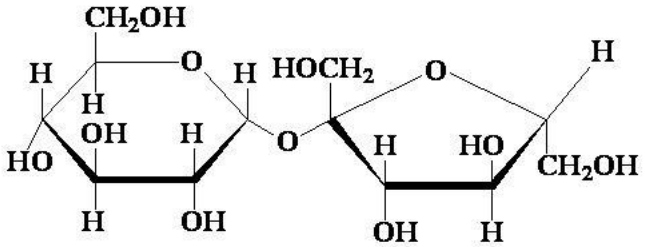
Glucose, Fructose, Sucrose Structure



glucose

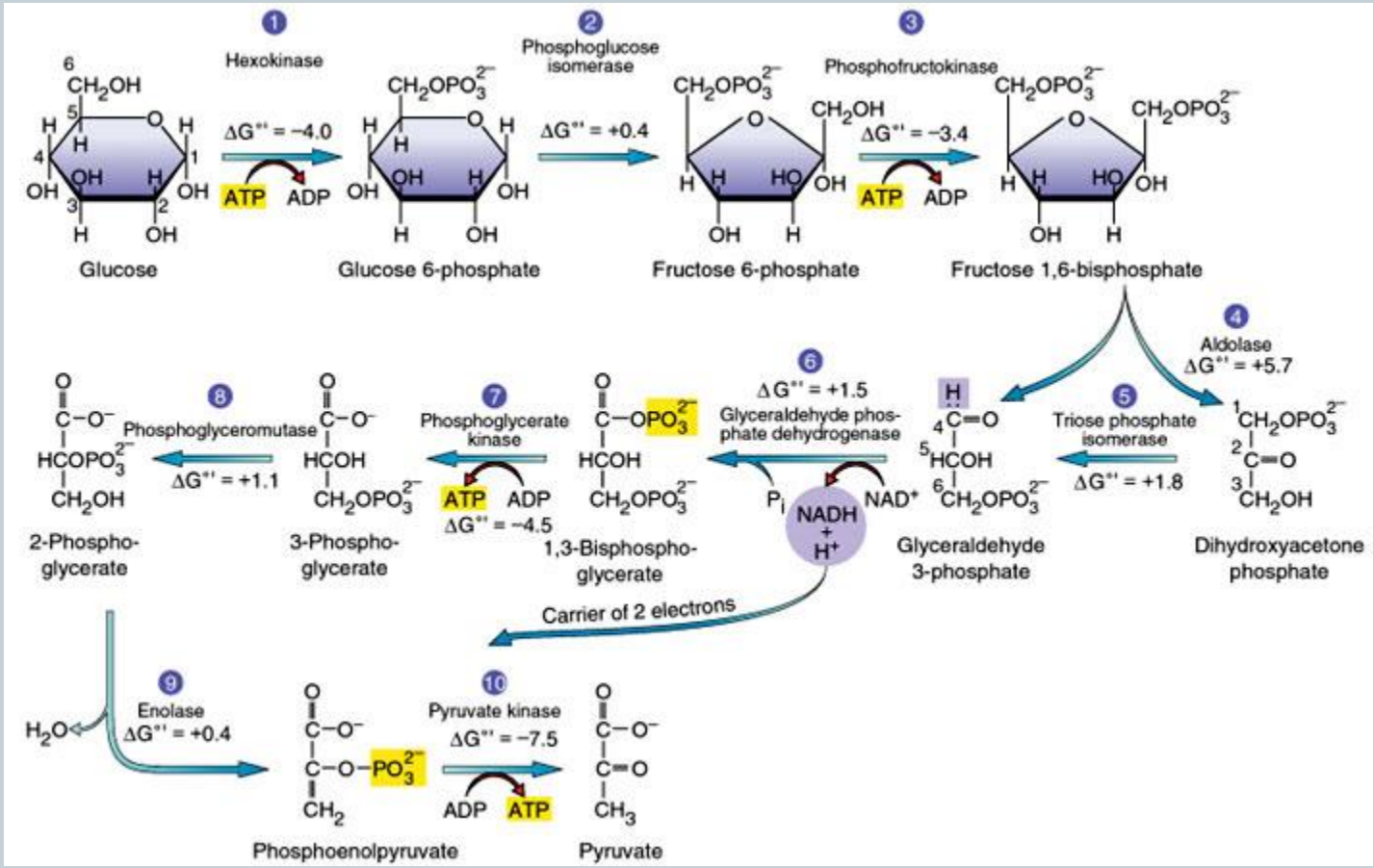


fructose

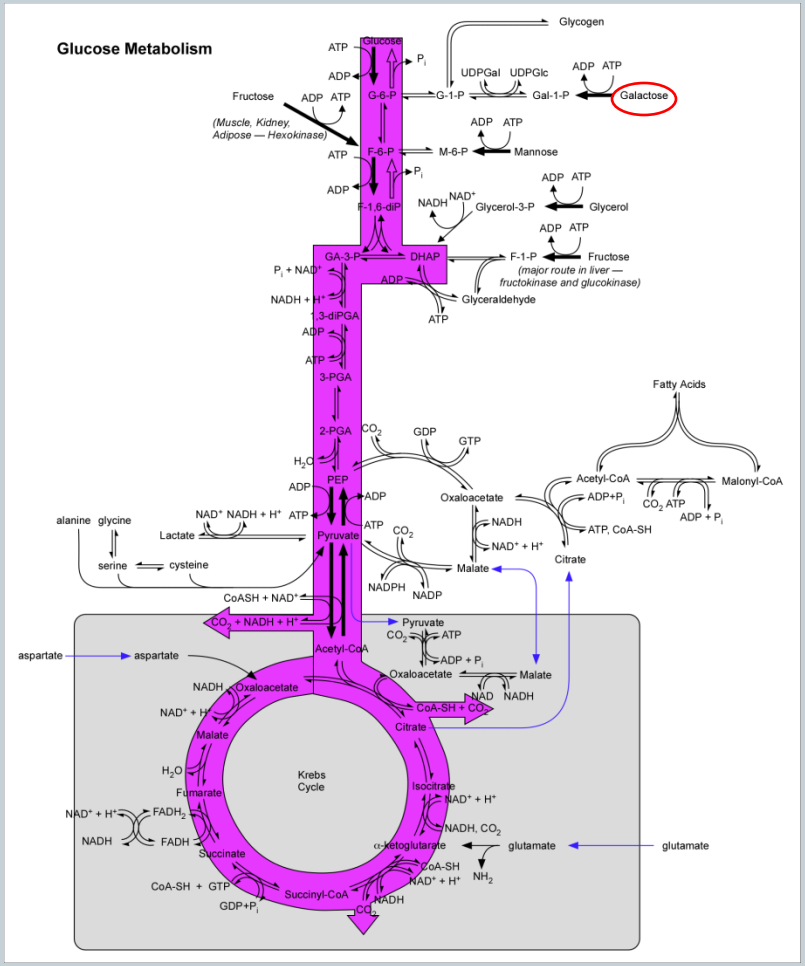


sucrose

Glycolysis

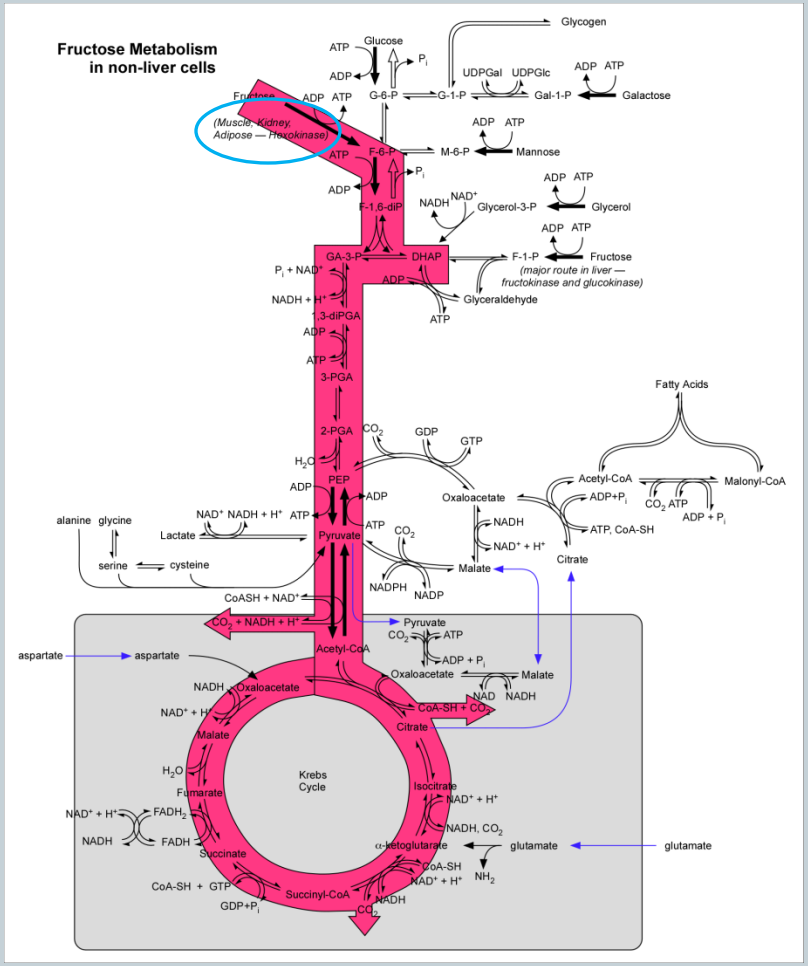

1
Hexokinase
ΔG°' = −4.0
ATP
ADP
Glucose
2
Phosphoglucose isomerase
ΔG°' = +0.4
Glucose 6-phosphate
3
Phosphofructokinase
ΔG°' = −3.4
ATP
ADP
Fructose 6-phosphate
Fructose 1,6-bisphosphate
4
Aldolase
ΔG°' = +5.7
5
Triose phosphate isomerase
ΔG°' = +1.8
Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
6
ΔG°' = +1.5
Glyceraldehyde phosphate dehydrogenase
Pi
NAD+
NADH + H+
1,3-Bisphospho-glycerate
7
Phosphoglycerate kinase
ATP
ADP
ΔG°' = −4.5
3-Phospho-glycerate
8
Phosphoglyceromutase
ΔG°' = +1.1
2-Phospho-glycerate
Carrier of 2 electrons
9
Enolase
ΔG°' = +0.4
H2O
Phosphoenolpyruvate
10
Pyruvate kinase
ΔG°' = −7.5
ADP
ATP
Pyruvate

Glucose Metabolism



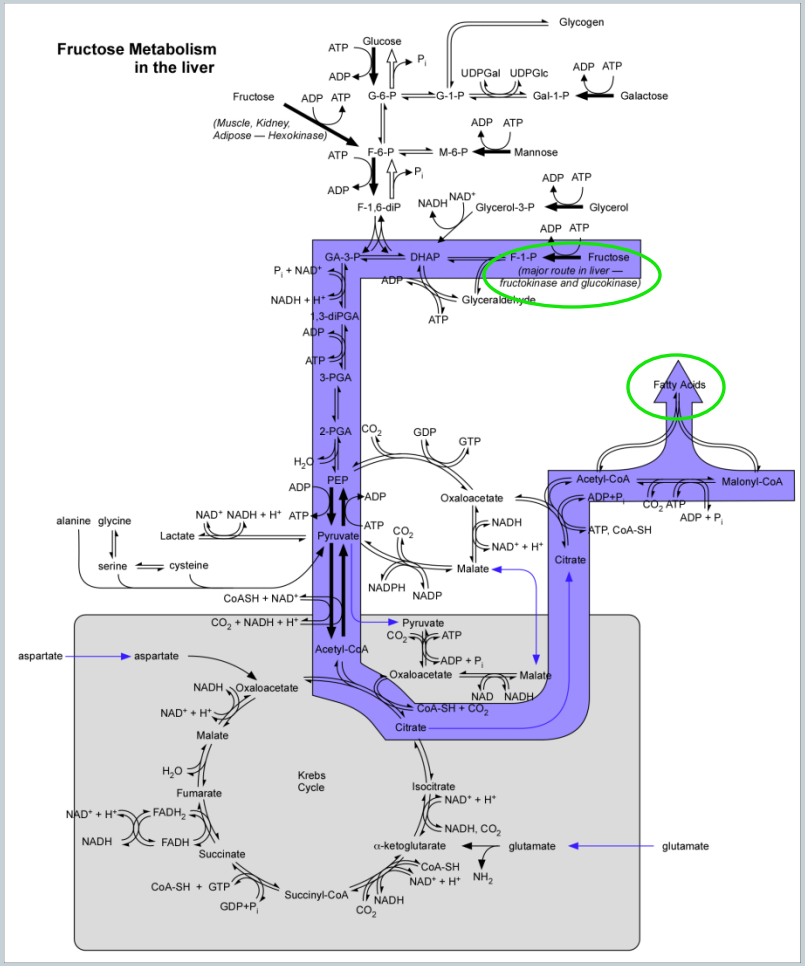
Bonner JJ, Indiana University. Obesity, Type 2 Diabetes, and Fructose. Available at http://www.indiana.edu/~oso/Fructose/MolBiol.html. Accessed January 10, 2012.

Fructose Metabolism in Non-Liver Cells

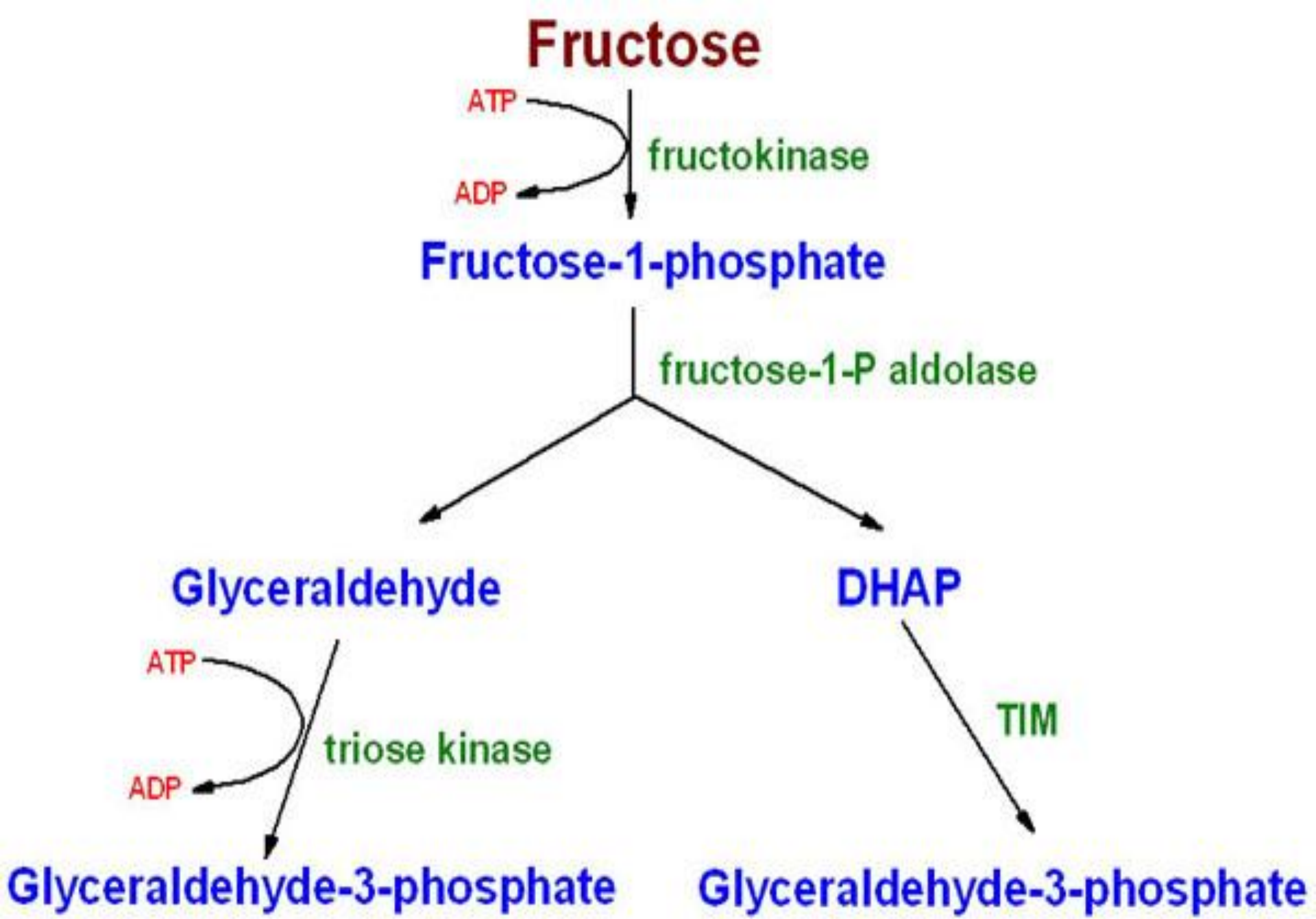


Bonner JJ, Indiana University. Obesity, Type 2 Diabetes, and Fructose. Available at http://www.indiana.edu/~oso/Fructose/MolBiol.html. Accessed January 10, 2012.

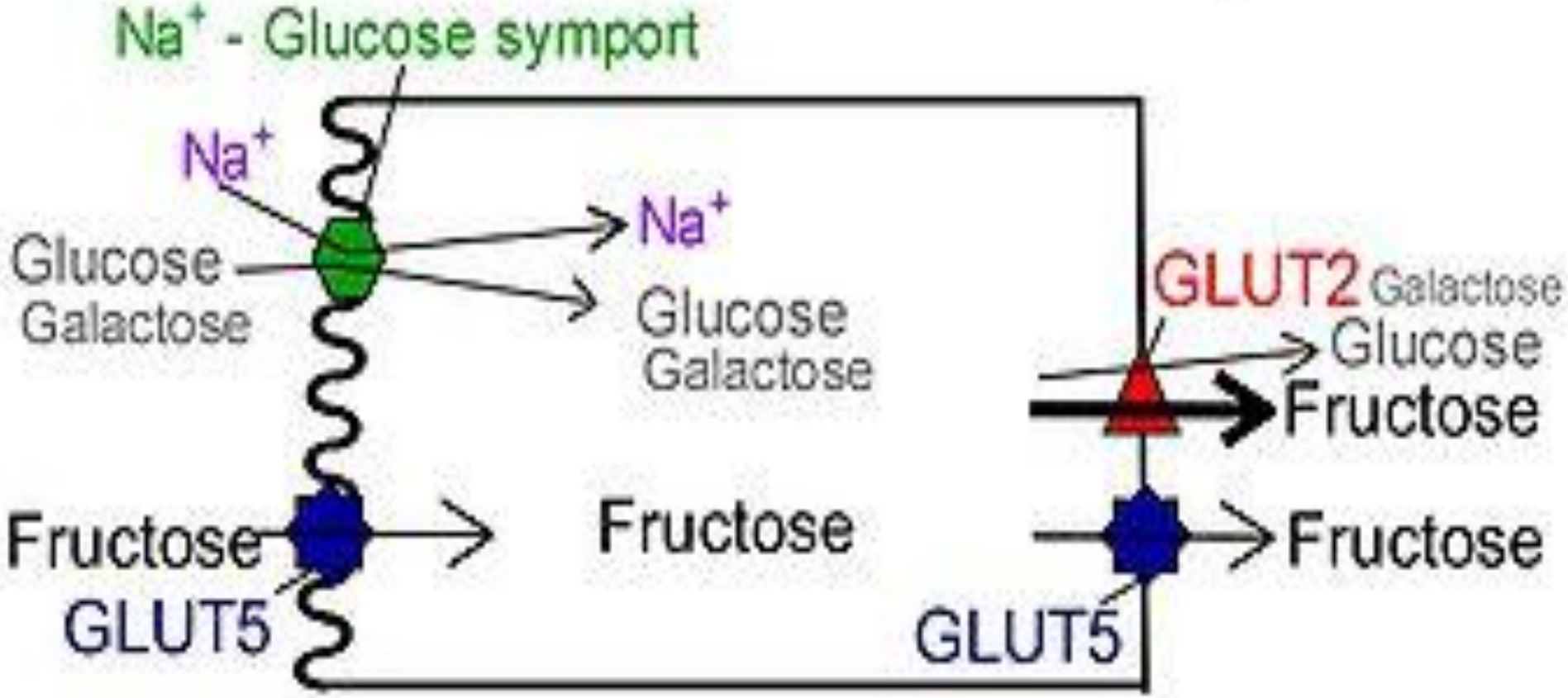
Fructose Metabolism in Liver Cells

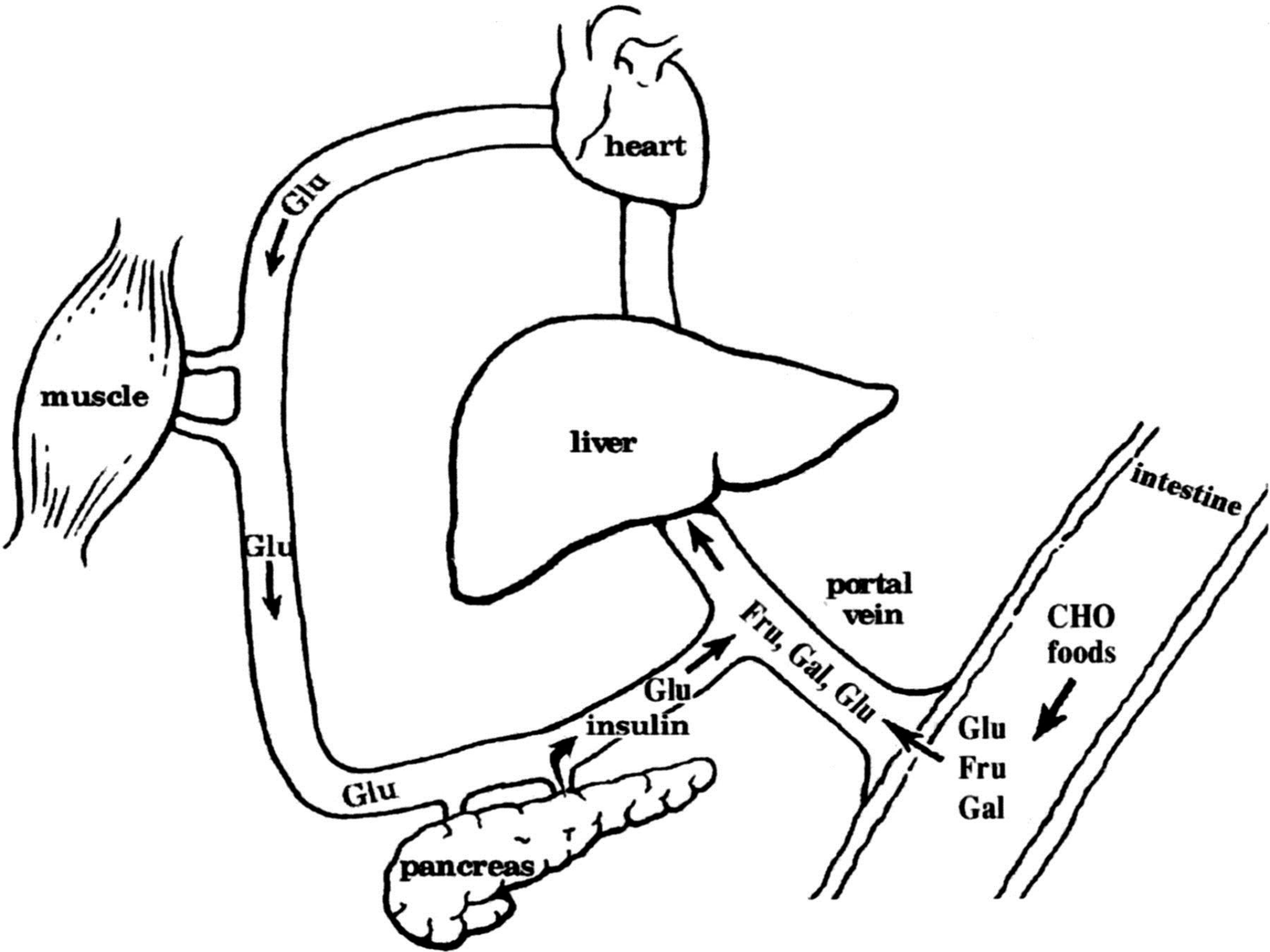


Bonner JJ, Indiana University. Obesity, Type 2 Diabetes, and Fructose. Available at http://www.indiana.edu/~oso/Fructose/MolBiol.html. Accessed January 10, 2012.

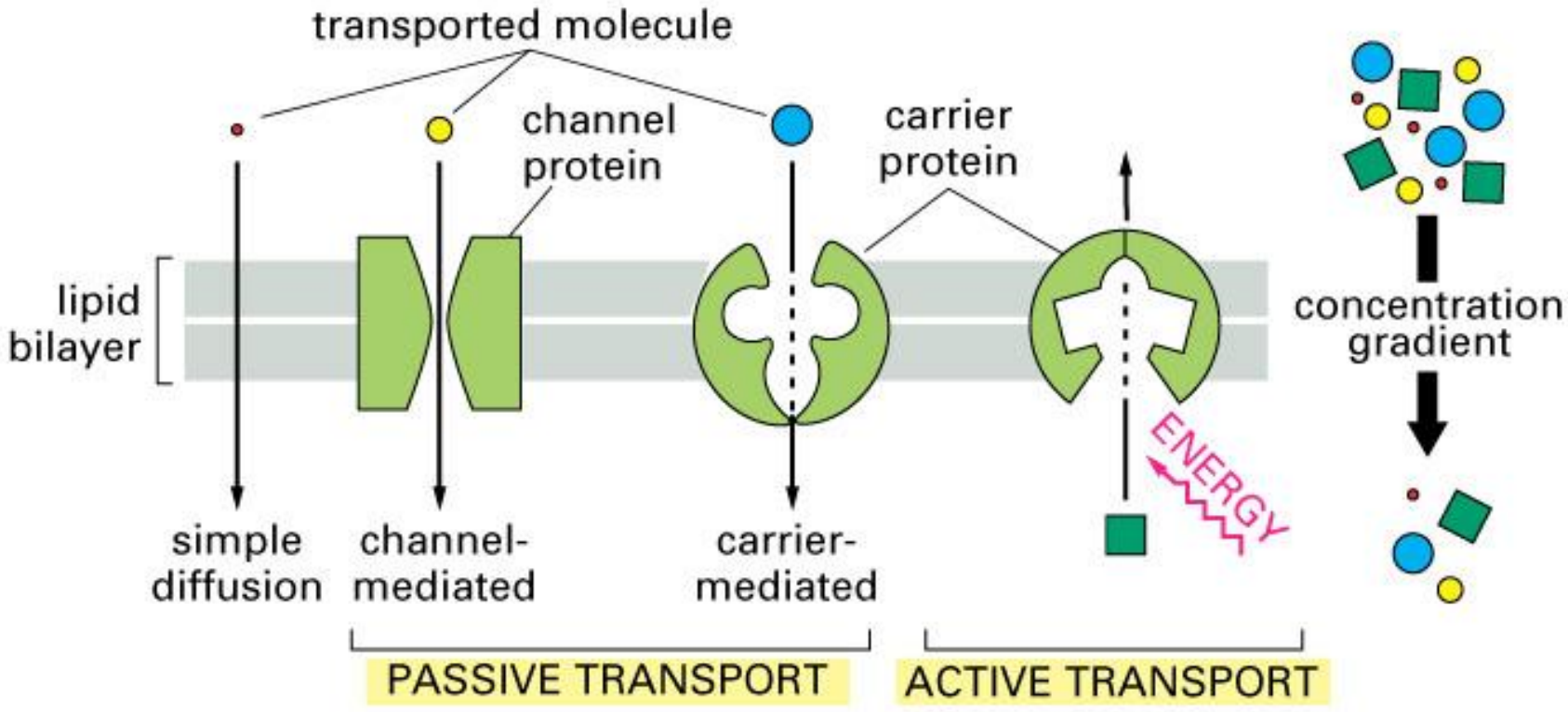


Fructose Transport




heart
Glu
muscle
liver
Glu
intestine
portal
vein
CHO
foods
Fru, Gal, Glu
Glu
insulin
Glu
Fru
Gal
Glu
pancreas

Intestinal Mucosa

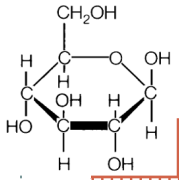


Blood

Figure 12-4 Essential Cell Biology, 2/e. (© 2004 Garland Science)

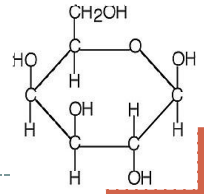
Transporter Protein	Insulin Regulatable	Major Sites of Expression
GLUT1	NO	Erythrocytes, blood brain barrier, placenta, fetal tissues in general
GLUT2	NO	Liver, β-cells of pancreas, kidney, small intestine
GLUT3	NO	Brain, neurons
GLUT4	YES	Muscles, heart, brown and white adipocytes
GLUT5	NO	Intestine, testis, kidney
GLUT6	NO	Spleen, leukocytes, brain
GLUT7	NO	Unknown
GLUT8	NO	Testis, blastocyst, brain
GLUT9	NO	Liver, kidney
GLUT10	NO	Liver, pancreas
GLUT11	NO	Heart, muscle
GLUT12	NO	Heart, prostate

Gropper SS, Smith JL, Groff JL. Carbohydrates. In: Advanced Nutrition and Human Metabolism. 5th ed. Belmont, CA: Wadsworth, Cengage Learning; 2009: 72.



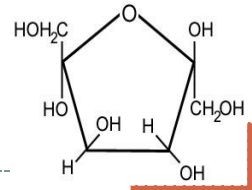
Glucose

- Active transport
- Dependent on Na/K-ATPase pump
- SGLT1 carrier
- Transported from cell into circulation by GLUT2
- 4 kcal/g



Galactose

- Active transport
- Dependent on Na/K-ATPase pump
- SGLT1 carrier
- Transported from cell to liver by GLUT2
- Absorbed by liver so there is no circulating blood galactose
- Not subject to hormonal regulation
- 4 kcal/g



Fructose

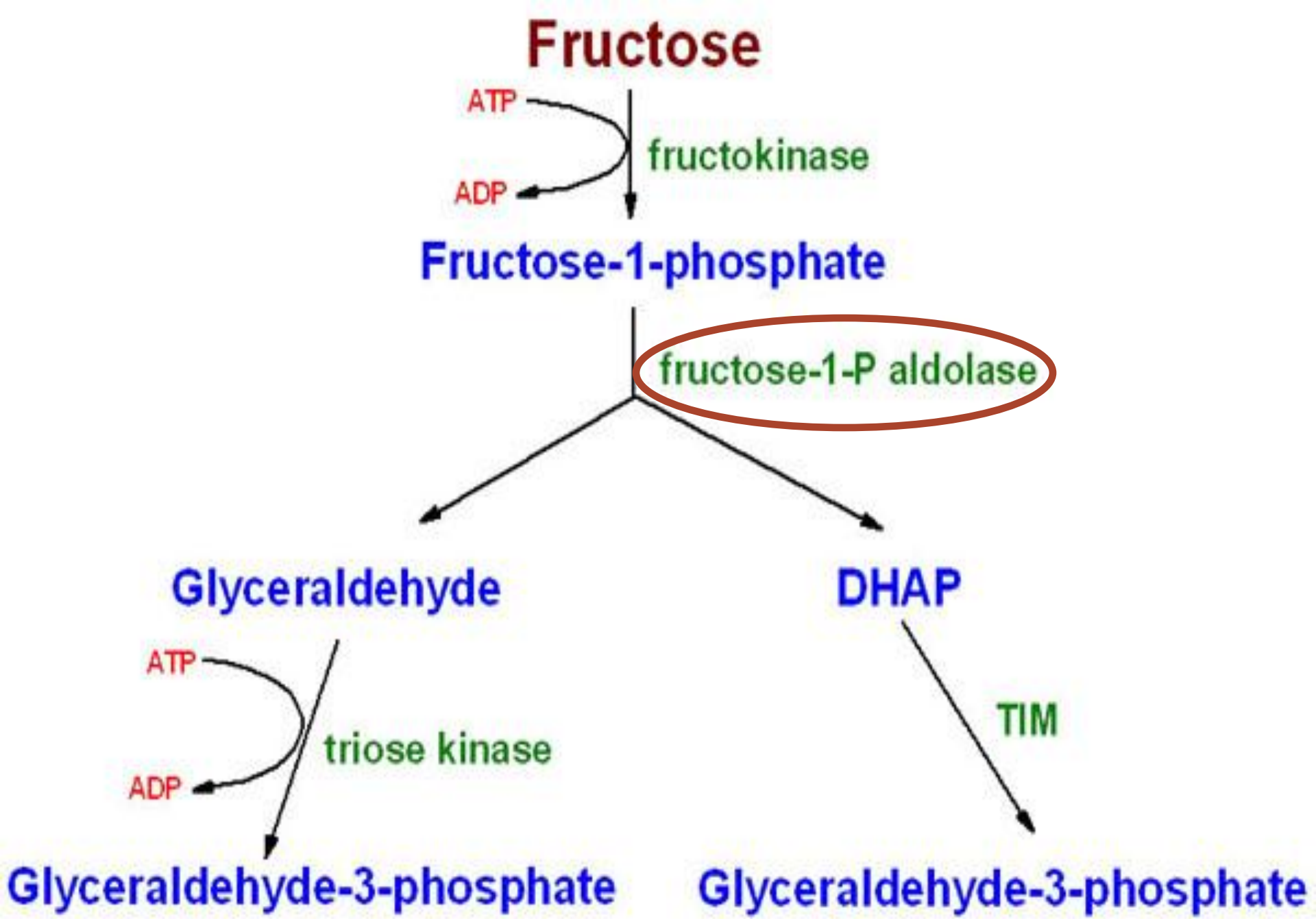
- Facilitated transport
- GLUT5
- Slower rate of absorption, but empties stomach quicker
- Can use GLUT2, but dependent on glucose concentration
- Absorbed by liver so there is no circulating blood fructose
- Not subject to hormonal regulation
- 4 kcal/g

Role of Fructose in IBS/Journal Article

Fructose Malabsorption—Fructosemia (hereditary fructose intolerance)

- 1-phosphofructaldolase
- Autosomal recessive disease
- Hypoglycemia; progressive liver disease
- Exclude:
  - Fructose
  - Sucrose
  - Sorbitol
  - Invert sugar
  - Maple syrup; honey; molasses
  - Foods high in fructans

Escott-Stump S. Inborn errors of carbohydrate metabolism. In: Nutrition and Diagnosis-Related Care. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2008; 167-169.



Fructose Malabsorption Non-hereditary

- Fructose fermented by bacteria in intestine to give off hydrogen or methane
- FODMAPs
  - Fermentable oligo-, di-, and monosaccharides and polyols **(short-chain carbohydrates)**
- FODMAPs known to cause abdominal pain, bloating, distension, altered bowels, nausea, vomiting

How do they diagnose fructose malabsorption?

- Not a consensus
- ≥20 ppm
- Positive symptoms
- Peak at 1.5-3 hrs
- 25 g or higher

Kyaw MH, Mayberry JF. Fructose malabsorption: True condition or a Variance from normality. *Journal of Clinical Gastroenterology*. 2011;45:16-20.

Ghoshal UC. How to interpret hydrogen breath tests. *Journal of Neurogastroenterol Motil*. 2011; 17:312-317.

Saad RJ, Chey WD. Breath Tests for Gastrointestinal Disease: The Real Deal or Just a lot of Hot Air? *Gastroenterology(Imaging and Advanced Technology)*. 2007; 133:1763-1766.

Latulippe ME, Skoog SM. Fructose Malabsorption and Intolerance: Effects of Fructose with and without Simultaneous Glucose Ingestion. *Critical Reviews in Food Science and Nutrition*. 2011; 51:583-592.

What is IBS?

- Abdominal pain/discomfort with altered bowel habits
- 3 types
  - Diarrhea prominent
  - Constipation prominent
  - Alternating
- No known medical cause
- ≥ 3 months of continuous or recurrent symptoms with altered stools
- R/O other conditions, like Crohn's or celiac
- 10-15% of the U.S. population
- One of the most common 'functional' GI disorders, representing 3% of all primary care consultations

Escott-Stump S. Irritable Bowel Syndrome. In: Nutrition and Diagnosis-Related Care. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2008; 409-411.

Comparison of breath testing with fructose and high fructose corn syrup in health and IBS

Purpose

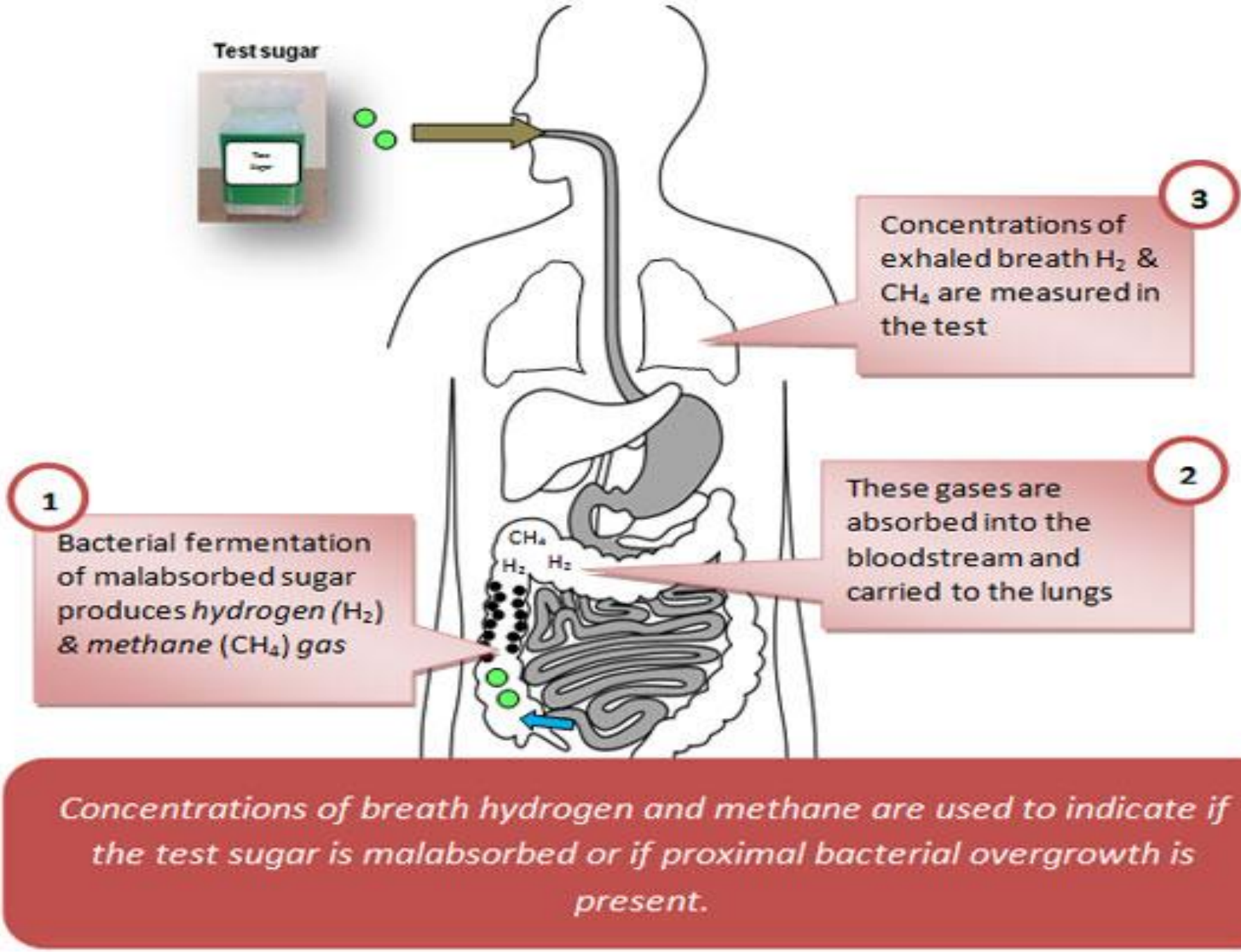
- Grade I
- "Our hypothesis was that fructose intolerance (i.e. positive hydrogen breath test and gastrointestinal symptoms) would occur more frequently with pure fructose compared to fructose provide as HFCS in healthy subjects and in IBS."

Skoog SM, Bharucha AE, Zinsmeister AR. Comparison of breath testing with fructose and high fructose corn syrups in health and IBS. *Neurogastroenterol Motil*. 2008;20:505-511.

Hydrogen Breath Test

- Alternative to the invasive, expensive endoscopy
- Works by measuring the hydrogen expelled due to the gut bacteria fermenting the carbohydrate substrate

Ghoshal UC. How to interpret hydrogen breath tests. *Journal of Neurogastroenterol Motil*. 2011; 17:312-317.


Test sugar
3
Concentrations of exhaled breath H_2 & CH_4 are measured in the test
2
These gases are absorbed into the bloodstream and carried to the lungs
1
Bacterial fermentation of malabsorbed sugar produces *hydrogen* (H_2) & *methane* (CH_4) *gas*
CH_4
H_2
H_2
Concentrations of breath hydrogen and methane are used to indicate if the test sugar is malabsorbed or if proximal bacterial overgrowth is present.

Limitations

- False-positives
  - Smoking
  - Poor oral hygiene
  - If test subjects do not brush teeth and rinse with antibacterial mouthwash
  - Eating fermentable carbohydrates like pasta/bread
  - Physical exertion/hyperventilation
- Some produce methane
- The test lasts 3-5 hrs
- Lack of uniformity in interpreting results

Saad RJ, Chey WD. Breath Tests for Gastrointestinal Disease: The Real Deal or Just a lot of Hot Air? *Gastroenterology(Imaging and Advanced Technology)*. 2007; 133:1763-1766.

Methods

- Double-blind, randomized, crossover study
- 20 healthy subjects; 30 patients
- HBT
- Given 1 of 2 sugar solutions
  - 40 g fructose in 330 mL tap water (12%)
  - 40 g fructose as 95 g HFCS-55 in tap water for total 600 mL (12%)
- HFCS solution mimicked two cans of cola
- Breath samples every 30 minutes for 3 hrs using modified Haldane-Priestly bag
- Fructose malabsorption was defined as a rise in breath hydrogen of ≥20 ppm over the baseline value

Patient breakdown

- Diarrhea predominant IBS—12
- Constipation predominant IBS—4
- Alternating IBS—10
- Functional diarrhea—4

Symptoms

- Visual Analog Scales (VAS)
- Every 30 min for 3 hrs
- 10 mm increase in symptom scores was considered abnormal
- Bristol scale
- Done for both sugar solutions

VAS and Bristol Stool Chart

c. Visual Analog Scale (VAS)[2]

No pain — Pain as bad as it could possibly be

[1] If used as a graphic rating scale, a 10 cm baseline is recommended.
[2] A 10 cm baseline is recommended for VAS scales.

Bristol Stool Chart

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces. **Entirely Liquid**

Statistical Analysis

- McNemar's test for paired discrete data
- Paired t-tests used to compare AUC for hydrogen breath excretion after fructose and HFCS
- Relationship between symptoms and breath hydrogen tests were analyzed using Spearman's correlation coefficient
- Breslow-Day test used to compare the association between health and IBS
- All stats analysis carried out using SAS software

Results

Variable	Controls (n=20)	Patients (n=30)
Age (yrs) (mean ± SE)	28 ± 3	41 ± 2
Number of females	14 (60)	21 (60)
BMI (mean ± SE)	24 ± 1	26 ± 1
Breath hydrogen test		
Abnormal—fructose	**13 (65)**	**21 (70)**
Abnormal—HFCS	**4 (20)**	**9 (30)**
Abnormal—fructose and HFCS	**4 (20)**	**9 (30)**
Normal—fructose and HFCS	7 (35)	9 (30)
Symptoms after fructose		
Flatulence	4(20)	9 (30)
Bloating	5 (25)	10 (33)
Nausea	2 (10)	8 (27)
Abdominal pain	2 (10)	9 (30)
Symptoms after HFCS		
Flatulence	2 (10)	6 (20)
Bloating	1 (5)	10(33)
Nausea	0	8 (27)
Abdominal pain	0	9 (30)

All values except age and BMI are *N* (%) of group total. HFCS, high fructose corn syrup; BMI, body mass index.

Comparison of symptoms and breath hydrogen response in controls and IBS

Variable	Control (n=20)	Patients (n=30)
Normal fructose breath test	7	9
Number with symptoms	**2/7**	**3/9**
Abnormal fructose breath test	13	21
Number with symptoms	**5/13**	**12/21**
Normal HFCS breath test	16	21
Number with symptoms	**2/16**	**12/21**
Abnormal HFCS breath test	4	9
Number with symptoms	**0/4**	**2/9**

Discussion of fructose and HFCS

- 65% healthy subjects and 70% patients incompletely absorbed pure fructose
- 20% healthy subjects and 30% patients incompletely HFCS
- Other studies found similar results
- Fructose intolerance may be present in a minority

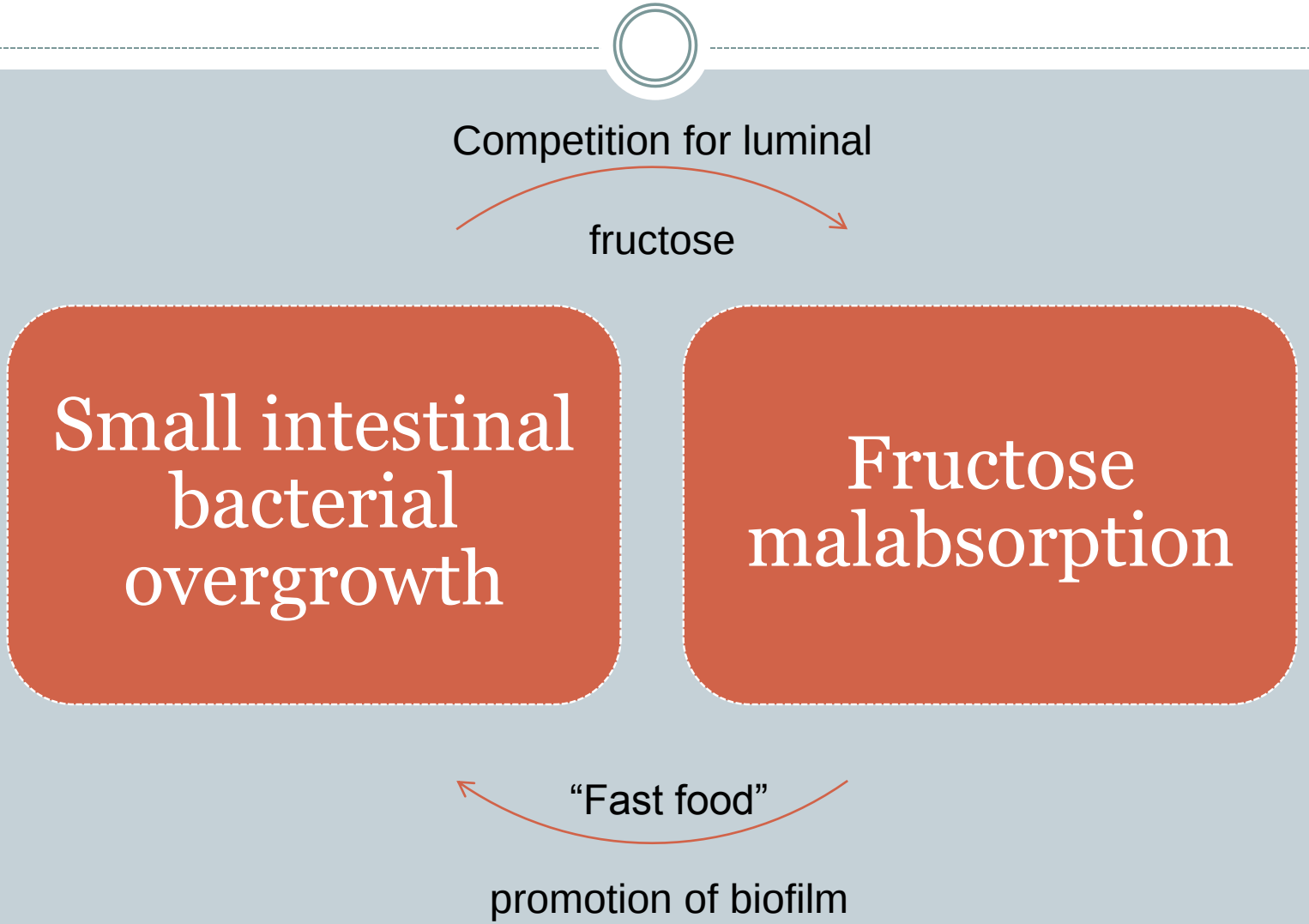
Discussion of HBT

- HBTs may overestimate prevalence of fructose malabsorption at 25 g d/t being unrealistic
- Suggest using smaller fructose dose

Discussion of Conclusions

- Glucose increases fructose absorption
- Fructose intolerance is more prevalent after fructose alone than after HFCS in health and IBS
- Prevalence of fructose intolerance is not significantly different between health and IBS

Theoretical Relationship



Gibson PR, Newnham E, Barrett JS, Shepherd SJ, Muir JG. Review article: Fructose malabsorption and the bigger picture. *Alimentary Pharmacology and Therapeutics*. 2007; 25:349-363.

Solutions/MNT for IBS/fructose malabsorption

Medical Approaches

- Anemia, fever, persistent diarrhea, rectal bleeding, weight loss, infections, and nocturnal symptoms
- Medications only if nonprescription methods do not work
- Antibiotics
- Psychotherapy/antidepressants
- Be aware of pain, constipation, and diarrheal medications

Escott-Stump S. Irritable Bowel Syndrome. In: Nutrition and Diagnosis-Related Care. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2008; 409-411.

MNT

- Most IBS patients attribute their symptoms to a food sensitivity
- Identify the culprit
- ADA (AND) suggests 3 dietitian visits
- Increase physical activity, fluid, and fiber
- Food diary
- Avoid high-fat and high sugar
- Avoid spicy or gas-forming oligosaccharides, like Brussels sprouts, cabbage, beans
- Ensure adequate quantity of food intake

Escott-Stump S. Irritable Bowel Syndrome. In: Nutrition and Diagnosis-Related Care. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2008; 409-411.

FODMAP elimination diet

- Lactose
- Fructose
- Fructans (also called inulin, fructo-oligo-saccharide, or oligofructose)
- Sugar alcohols
- Galactans

Barrett JS, Irving PM, Shepherd SJ, Muir JG, Gibson PR. Comparison of the prevalence of fructose and lactose malabsorption across chronic intestinal disorders. *Alimentary Pharmacology & Therapeutics*. 2009; 30:165-174.

FODMAPs elimination diet—what can you eat??

- Lactose-free dairy
- Small servings of berries and citrus fruits
- Potatoes, rice, oats, corn products
- Lean meats
- Salad vegetables
- Plant based oils
- Very small servings of sugar, honey, or syrup

Patsy Catsos. Irritable Bowel Syndrome Health Center. Available at http://www.webmd.com/ibs/features/finding-right-diet-ibs?page=3. Accessed January 10, 2012.

Handouts

- A Community for Irritable Bowel Syndrome and Digestive Health Sufferers. Available at http://www.ibsgroup.org/brochures/fodmap-intolerances.pdf. Accessed January 10, 2012.
- Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: Guidelines for effective dietary management. *Journal of the American Dietetic Association*. 2006; 106: 1631-1639.
- Latulippe ME, Skoog SM. Fructose malabsorption and intolerance: Effects of fructose with and without simultaneous glucose ingestion. *Critical Reviews in Food Science and Nutrition*. 2011; 51:583-592.

How does it work?

- 1-2 wks eliminate all FODMAPs, including alcohol
- Reintroduce 1 FODMAP group at a time
- Goal: Find the elimination diet that works for that pt
- Perhaps they will be able to tolerate small amounts of foods they need to eliminate
- Dry wines tolerated best, beer has no fructose, hard liquors need to read label

Patsy Catsos. Irritable Bowel Syndrome Health Center. Available at http://www.webmd.com/ibs/features/finding-right-diet-ibs?page=3. Accessed January 10, 2012.

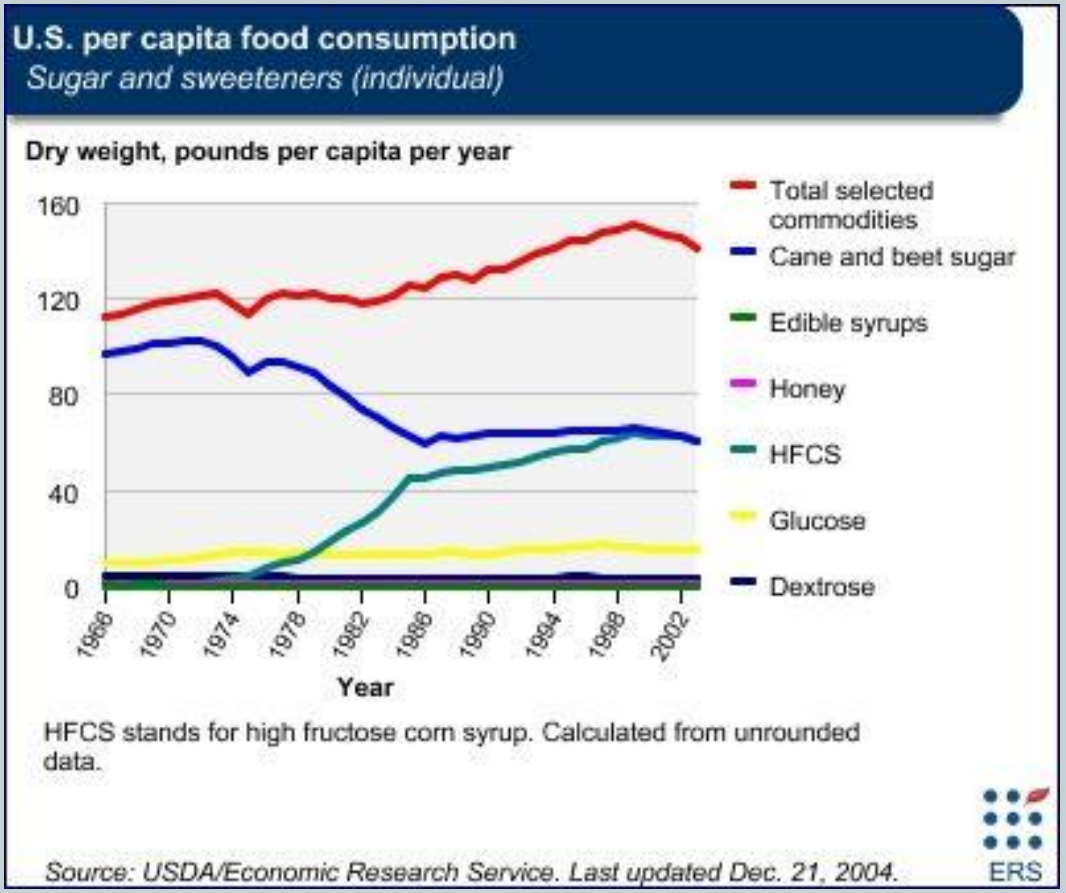
What HFCS has to do with IBS and the general population

High Fructose Corn Syrup

- Refined sweetener
- Introduced in the 1970s
- Treat cornstarch with acid and enzymes to break down the starch into glucose; different enzymes convert about half the glucose to fructose
- HFCS-55 (soft drinks)and HFCS-42 (beverages, processed foods, cereals, etc.)
- Corn sugar
- http://www.youtube.com/watch?v=jisBG3egS80

Insel P, Turner ER, Ross D. Carbohydrates, Nutritive Sweeteners. In: Nutrition. 3rd ed. Sudbury, MA: Jones and Bartlett Publishers; 2007; 165.

Comparison of Sugar and Sweetener Intake in America



Bonner JJ, Indiana University. Obesity, Type 2 Diabetes, and Fructose. Available at http://www.indiana.edu/~oso/Fructose/Fructose.html. Accessed January 10, 2012.

ADA Reports on HFCS

- Highest intake in adolescence
- Sweetened soft drinks make up 1/3 of added sugar intake
- 14-18 yrs
  - Carbonated soft drink intake exceeded milk and fruit drinks (2004)

American Dietetic Association. Position of the American Dietetic Association: Use of Nutritive and Nonnutritive Sweeteners. *Journal of the American Dietetic Association*. 2004; 104: 255-275.

Ability of the normal human small intestine to absorb fructose: evaluation by breath testing

- Purpose: To distinguish at what dose malabsorption happens in healthy subjects to determine an appropriate amount to diagnose fructose malabsorption.
- Tested both amount (15, 25, 50g) and concentration (10, 30%) in 20 healthy subjects

Rao SSC, Attaluri A, Anderson L, Stumbo P. Ability of the Normal Human Small Intestine to Absorb Fructose: Evaluation by Breath Testing. *Clinical Gastroenterology and Hepatology*. 2007; 5:959-963.

What happened?

- 15 g fructose dose
  - 20 out of 20 tolerated
  - No symptoms reported
- 25 g fructose dose
  - 18 out of 20 tolerated
  - No symptoms reported
- 50 g fructose dose at 10% concentration
  - 4 out of 20 absorbed
  - 69% with a positive breath test reported symptoms
  - 25% with a negative breath test reported symptoms
- 50 g fructose dose at 33% concentration
  - 8 out of 20 absorbed
  - 75% with a positive breath test reported symptoms
  - 25% with a negative breath test reported symptoms

What is this study saying about fructose malabsorption?

- BOTH a positive hydrogen breath test and symptoms
- Suggest 25 g dose to determine if malabsorption is present
- Food diary and dietary consult highly recommended
- Amount of fructose matters more than the concentration

What is the ADA saying about fructose/IBS/HFCS?

- When following nutrition recommendations, nutritive sweeteners can be consumed in moderation
- RD's role is to provide scientific evidence
- Obesity is caused by an entire host of factors
- Sucrose/fructose have GRAS status
- Malabsorption can be detected in 37% to 80% of healthy people at 50 g and in >70% of children to a 2 g/kg bw/d load
- Fructose is better absorbed as sucrose and worse when amount of fructose exceeds amount of glucose

American Dietetic Association. Position of the American Dietetic Association: Use of Nutritive and Nonnutritive Sweeteners. *Journal of the American Dietetic Association*. 2004; 104: 255-275.

What is the ADA saying about fructose/IBS/HFCS?

- Increase in consumption of HFCS "could have implications for absorption and lipid profiles in susceptible individuals."
- HFCS consumption may cause a hypertriglyceride effect
- There may be an association between sweeteners and obesity, but no "direct link"
- The concern that fructose/HFCS decreases insulin and leptin response needs further research
- Fructose is not recommended for diabetic patients d/t lipid effects
- RD needs to monitor intakes of fructose in relationship to GI dysfunction and hyperlipidemia

Questions

1. Has anyone ever tried the FODMAP diet on a patient?
2. Have RDs considered fructose as a condition that needs to be treated?
3. Will this information change the way you conduct your clinical work and educations?
4. Do you think that fructose malabsorption is often mistaken for something else, like lactose malabsorption or a gluten intolerance?

References

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- Alberts B, Bray D. How cells obtain energy from food. In: Essential Cell Biology. 3rd ed. New York, NY: Garland Science; 2010;425-452.
- American Dietetic Association. Position of the American Dietetic Association: Use of Nutritive and Nonnutritive Sweeteners. *Journal of the American Dietetic Association*. 2004; 104: 255-275.
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