BIOCHEMISTRY PATHWAY SERIES FOR STEP ONE

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For each pathway:

- Where do we start?
- Where do we end?
- What are the goals of the pathway?
- What key enzymes will get us from start to end, and what do they need to function?
- Key disorders related to these pathways
- How do they all come together?
- Summary: Special notes/therapeutics/key derivatives?

Fructose Metabolism

- **Start** with Fructose **end** with Glycerol and Glyceraldehyde 3-P
- **Goal** is to generate useable energy from fructose
- Key enzymes: Fructokinase, Aldolase B
- Disorders: Essential Fructosuria, Fructose Intolerance
- Fits into pathway for Glycolysis

FRUCTOKINASE

FRUCTOSE → FRUCTOSE-1-P

P

ATP ADP

ALDOLASE-B

DIHYDROXYACETONE-P

GLYCERALDEHYDE

NADH

NAD+

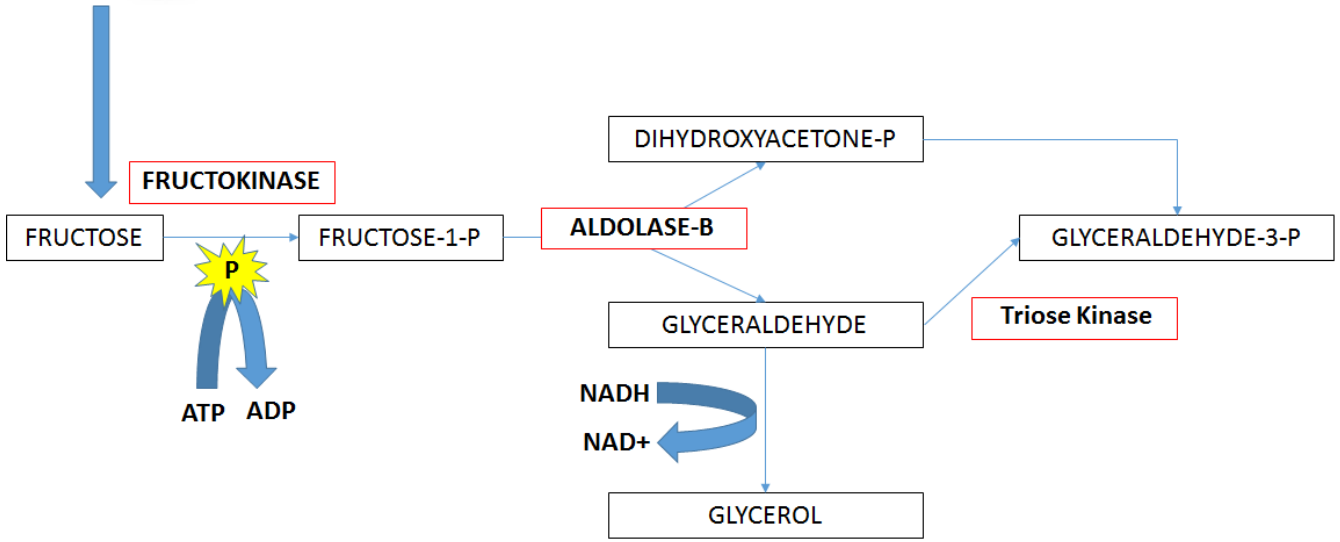
GLYCEROL

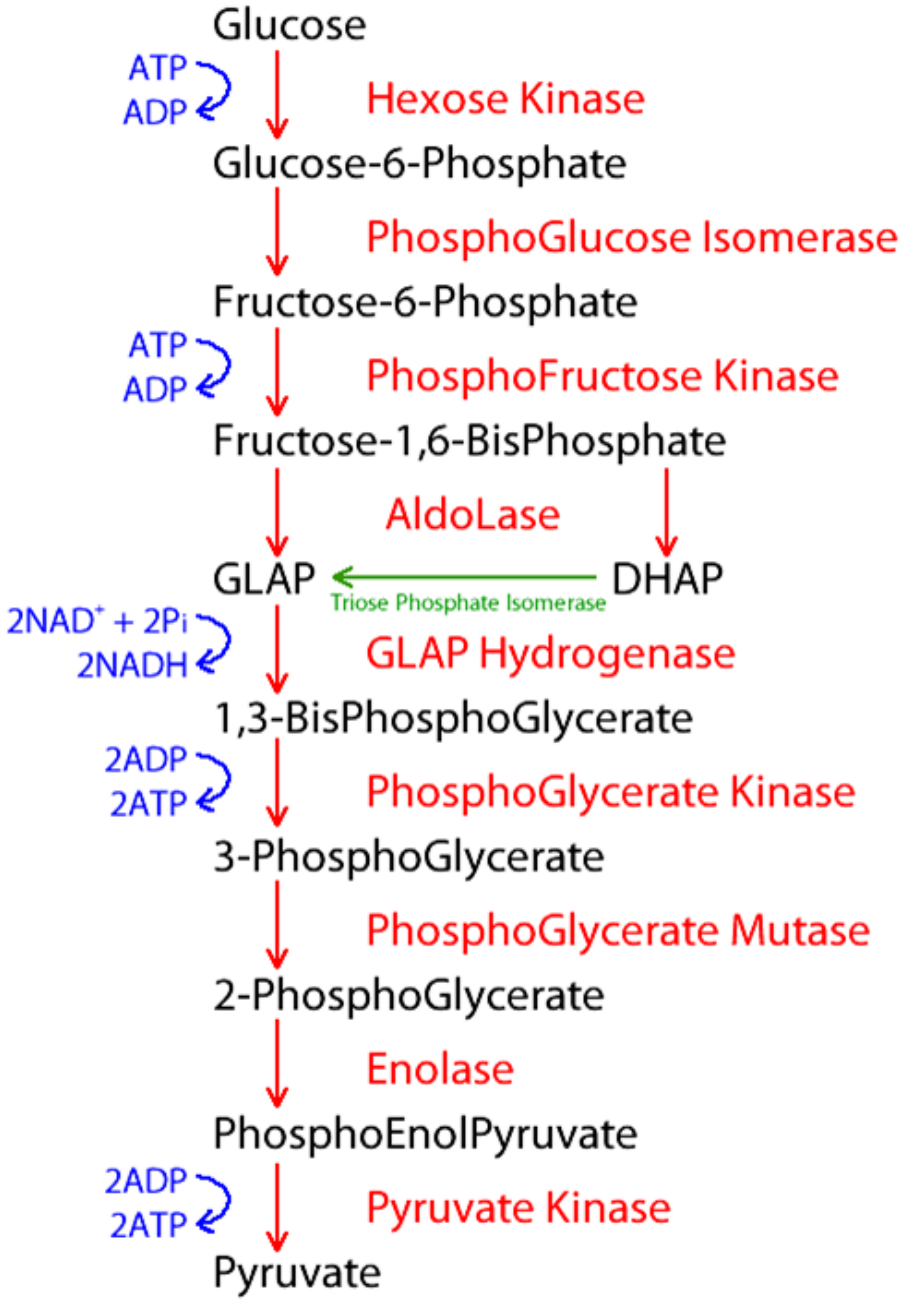
GLYCERALDEHYDE-3-P

Triose Kinase

GLYCOLYSIS

The Pathway: Overview





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GLYCERALDEHYDE

GLYCERALDEHYDE-3-P

Triose Kinase

NADH

NAD+

GLYCEROL

Glucose

ATP ADP — Hexose Kinase

Glucose-6-Phosphate

PhosphoGlucose Isomerase

Fructose-6-Phosphate

ATP ADP — PhosphoFructose Kinase

Fructose-1,6-BisPhosphate

AldoLase

DHAP

Triose Phosphate Isomerase

$2NAD^+ + 2Pi$ $2NADH$ — GLAP Hydrogenase

1,3-BisPhosphoGlycerate

2ADP 2ATP — PhosphoGlycerate Kinase

3-PhosphoGlycerate

PhosphoGlycerate Mutase

2-PhosphoGlycerate

Enolase

PhosphoEnolPyruvate

2ADP 2ATP — Pyruvate Kinase

Pyruvate

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ATP ADP

ALDOLASE-B

DIHYDROXYACETONE-P

GLYCERALDEHYDE

GLYCERALDEHYDE-3-P

Triose Kinase

NADH

NAD+

GLYCEROL

Glucose

ATP ADP — Hexose Kinase

Glucose-6-Phosphate

PhosphoGlucose Isomerase

Fructose-6-Phosphate

ATP ADP — PhosphoFructose Kinase

Fructose-1,6-BisPhosphate

AldoLase

GLAP ⟵ DHAP

Triose Phosphate Isomerase

2NAD+ + 2Pi

2NADH — GLAP Hydrogenase

1,3-BisPhosphoGlycerate

2ADP 2ATP — PhosphoGlycerate Kinase

3-PhosphoGlycerate

PhosphoGlycerate Mutase

2-PhosphoGlycerate

Enolase

PhosphoEnolPyruvate

2ADP 2ATP — Pyruvate Kinase

Pyruvate

For each pathway:

- Where do we start?
  - Fructose
- Where do we end?
  - Glycerol
  - Glyceraldehyde-3-P
- What are the goals of the pathway?
- What key enzymes will get us from start to end, and what do they need to function?
- Key disorders related to these pathways
- How do they all come together?

So what's the goal?

- Take a dietary sugar (fructose) and convert it into a product that can be used in cellular energy pathway (glycolysis)

- Problems in this pathway arise when enzymes are **missing** or **deficient**, leading to either a failure to utilize fructose or an accumulation of dangerous byproducts

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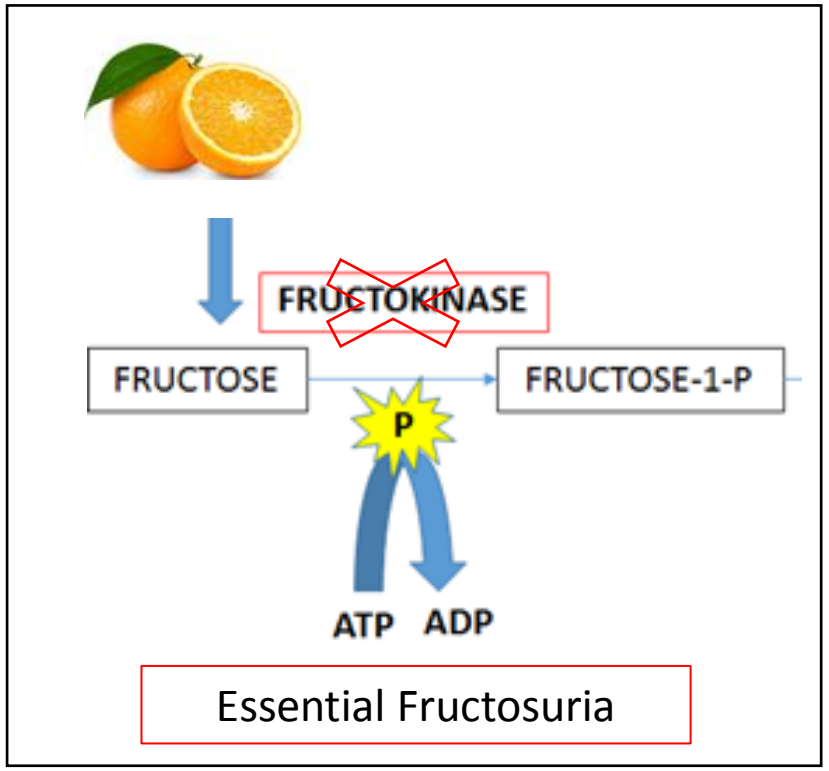
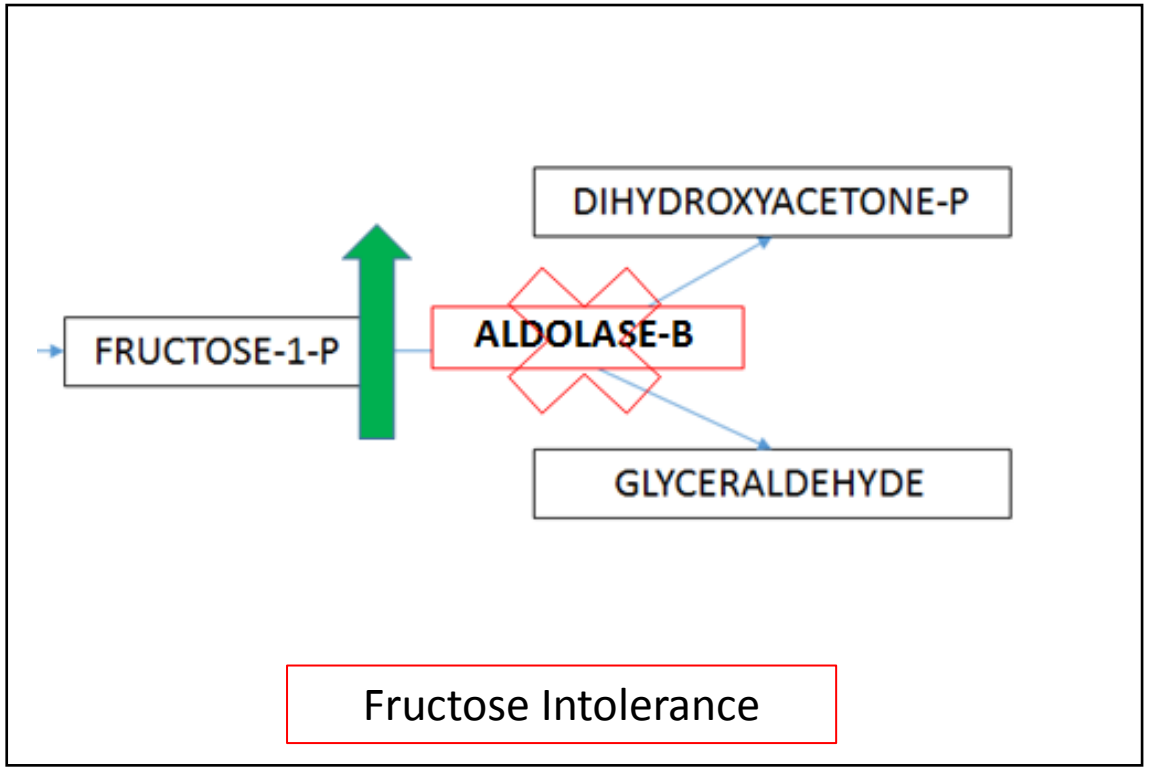
So what goes wrong and how does it present?

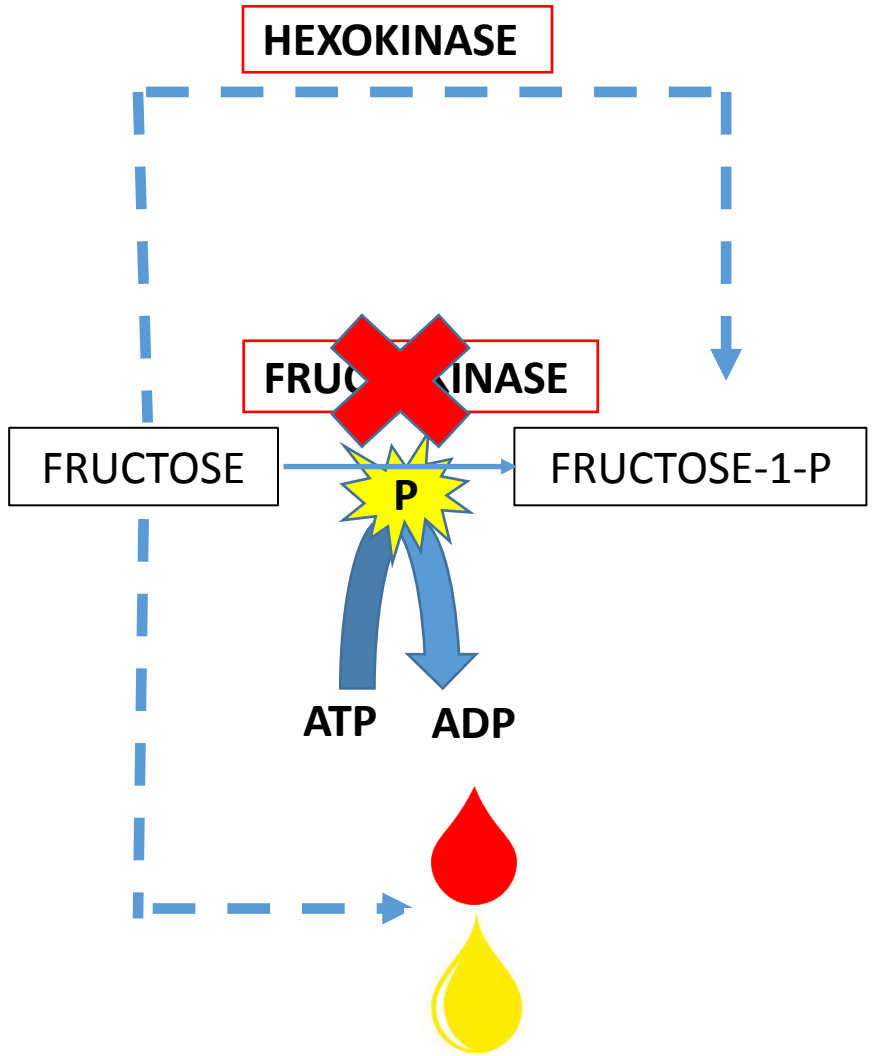
- Two conditions associated with this pathway: **Essential Fructosuria** and **Fructose Intolerance**
- Different enzymes are involved, vastly different clinical presentations





Essential Fructosuria

- Autosomal recessive condition that is essentially, fructose in the urine
- Lack of enzyme **fructokinase**, which converts **fructose** into **fructose-1-P**
- Without attached phosphate, fructose can't enter cells (just like our friend glucose), and can't be metabolized
- High levels of fructose in urine and blood



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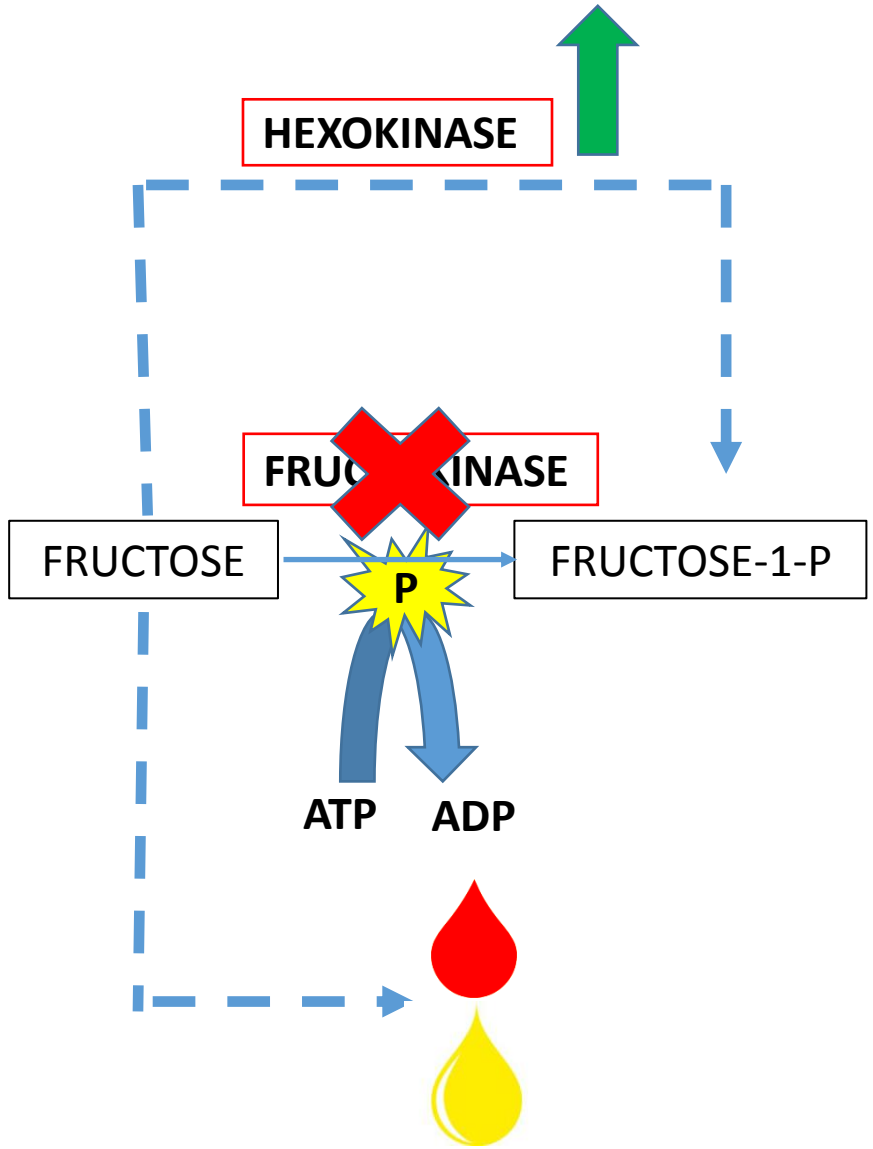
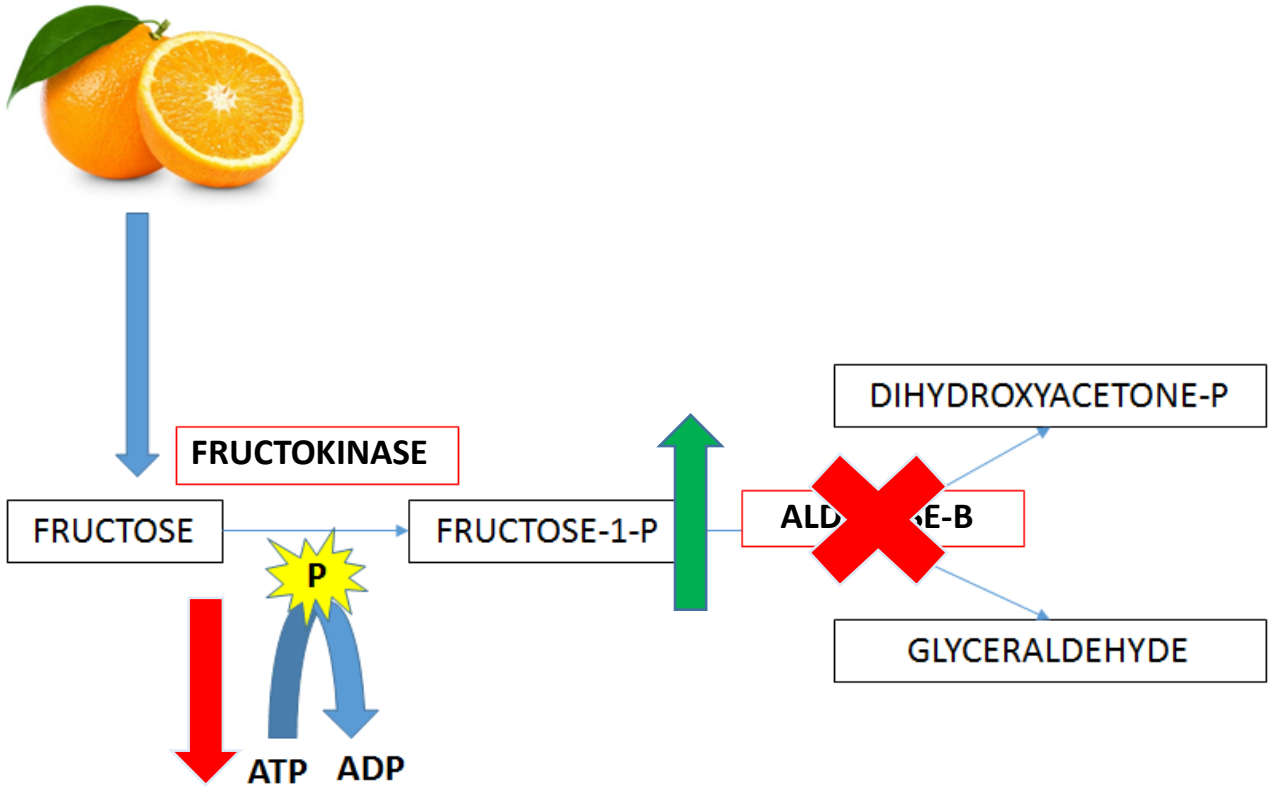
- Without attached phosphate, fructose can't enter cells (just like our friend glucose), and can't be metabolized
- High levels of fructose in urine and blood
- Activates **backup pathway**, where **hexokinase** is upregulated to produce small amounts of F1P, when then completes normal pathway
- **NO CLINICAL SYMPTOMS**, but Fructose is detected in blood and urine



Fructose Intolerance

- Autosomal Recessive lack of **Aldolase B**
- Cant convert Fructose 1-P to downstream products, causing it to accumulate
- Does **NOT** impact fructokinase, which keeps doing its thing
- Fructokinase keeps burning ATP to attach phosphate to Fructose, which is now “trapped” in cells with nowhere to go (makes phosphate sink)



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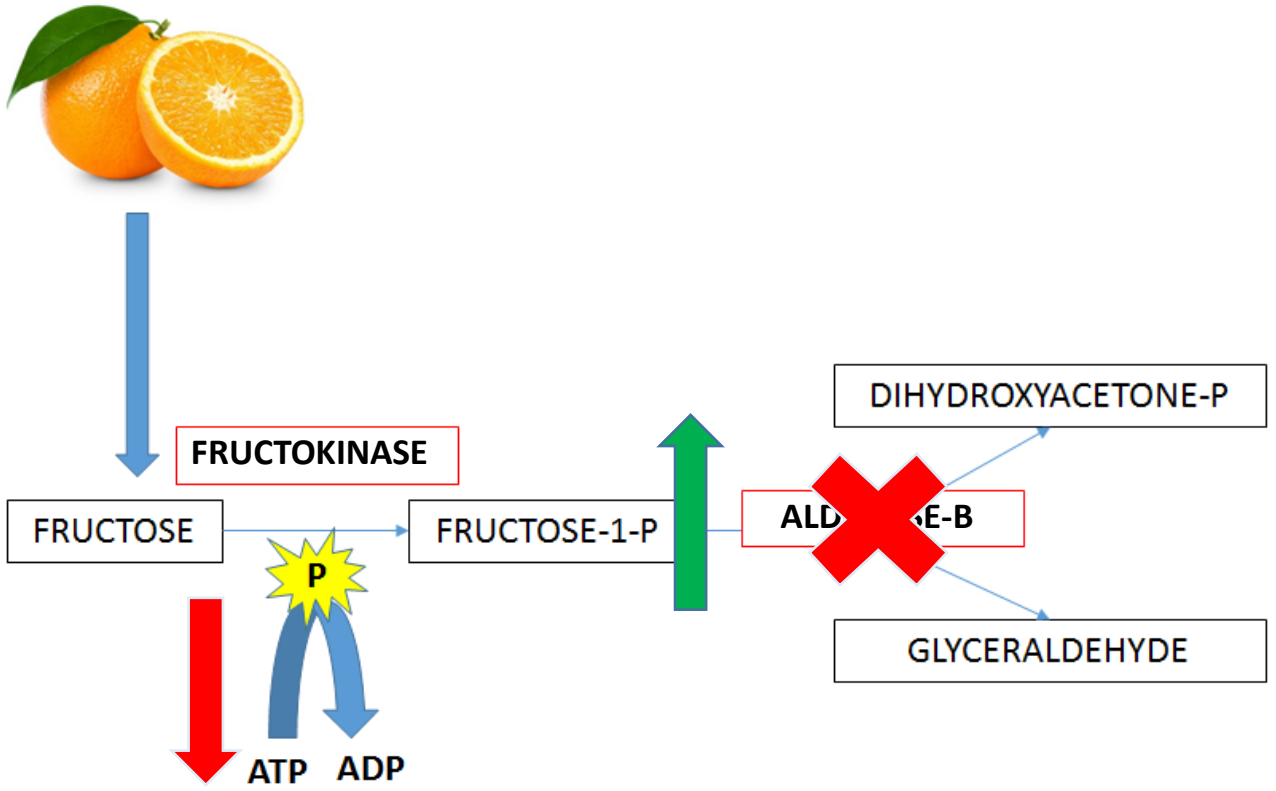
- Does **NOT** impact fructokinase, which keeps doing its thing
- Fructokinase keeps burning ATP to attach phosphate to Fructose, which is now “trapped” in cells with nowhere to go (makes phosphate sink)
- **Symptoms** relate to depletion of ATP and accumulation of F1P in liver cells whenever <u>fructose is consumed</u>: **Hypoglycemia, jaundice, hemorrhage, hepatomegaly, hyperuricemia**



For each pathway:

- Where do we start?
  - Fructose
- Where do we end?
  - Glycerol
  - Glyceraldehyde-3-P
- What are the goals of the pathway?
  - Convert dietary sugar (fructose) into a usable product for glycolysis
- What key enzymes will get us from start to end, (and what do they need to function)?
  - Fructokinase (→ Essential fructosuria)
  - Aldolase-B (→ Fructose intolerance)
- Key disorders related to these pathways
  - Essential Fructosuria (fructose in urine; generally asymptomatic; occasional hypoglyemia)
  - Fructose Intolerance (cellular injury from accumulation of F1P and ATP depletion)
- How do they all come together?
- Summary: Special notes/therapeutics/key derivatives?

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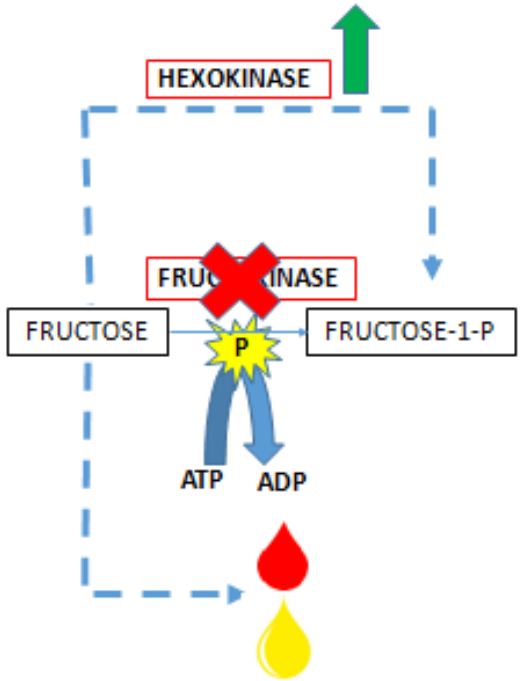
Presentations, Treatment, and Key Derivatives

- Essential Fructosuria: Urine smells sweet after a big meal of fruit, honey, etc. Worked up for diabetes and finds fructose in the urine instead of glucose. Runs in the family. No treatment required. Will likely ask about either pattern of inheritance (**recessive**) or missing enzyme (**fructokinse)**
  - **May** ask about what enzyme is upregulated in backup pathway (**hexokinase**)



Presentations, Treatment, and Key Derivatives

- Essential Fructosuria: Urine smells sweet after a big meal of fruit, honey, etc. Worked up for diabetes and finds fructose in the urine instead of glucose. Runs in the family. No treatment required.
  - Will likely ask about either pattern of inheritance (**dominant**) or missing enzyme (**fructokinse)**
  - **May** ask about what enzyme is upregulated in backup pathway (**hexokinase**)

- Fructose intolerance: Baby develops symptoms of lethargy, jaundice, vomiting, hypoglycemia after first meal containing fructose or sucrose (fruit, honey, etc). Treatment involves **AVOIDING FRUCTOSE AND SUCROSE**
  - Will likely ask about pattern of inheritance (**recessive)**, missing enzyme (**aldolase B**), or treatment

May ask question about how fructose enters glycolysis → Glyceraldehyde-3-P

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