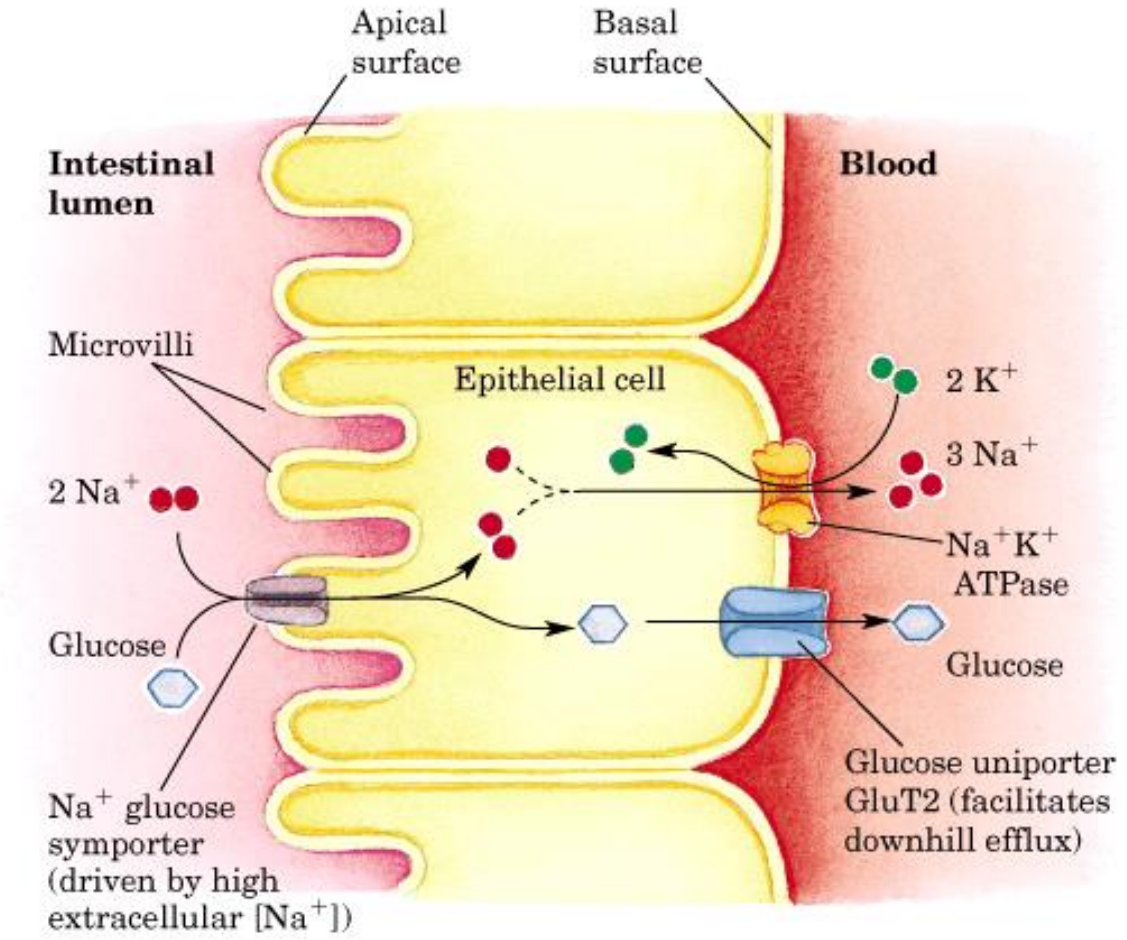
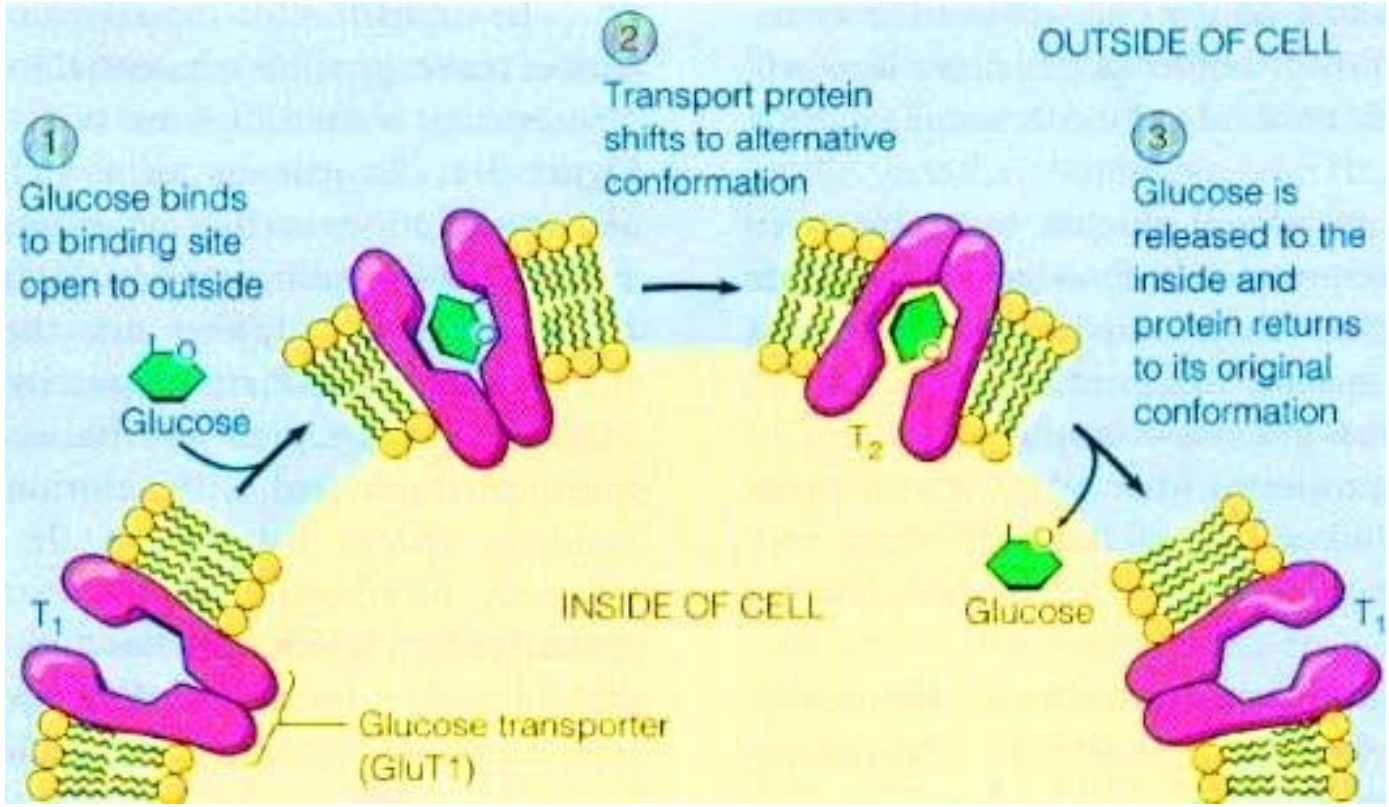
Normal Individuals

- Following digestion of disaccharides and polysaccharides, the monosaccharide Glucose is absorbed in the small intestine



Normal Individuals

- Direct Uptake of Glucose occurs in many cells of the body.
- Glucose in the blood stream is uptaken via Glucose transporters (GLUT, facilitated diffusion) and begins glycolysis



Normal Individuals

- **Indirect uptake of glucose occurs in the liver, skeletal muscle, and fat cells and is dependent upon insulin.**
- Insulin is secreted into the blood stream by the pancreatic beta-cells in response to increased blood glucose concentrations.
- Insulin binds to Insulin Receptors (IR, a Tyrosine Kinase Receptor) on the cell membranes of liver, skeletal muscle, and fat and causes receptor dimerization intracellular receptor phosphorylation.
- IR activation causes:

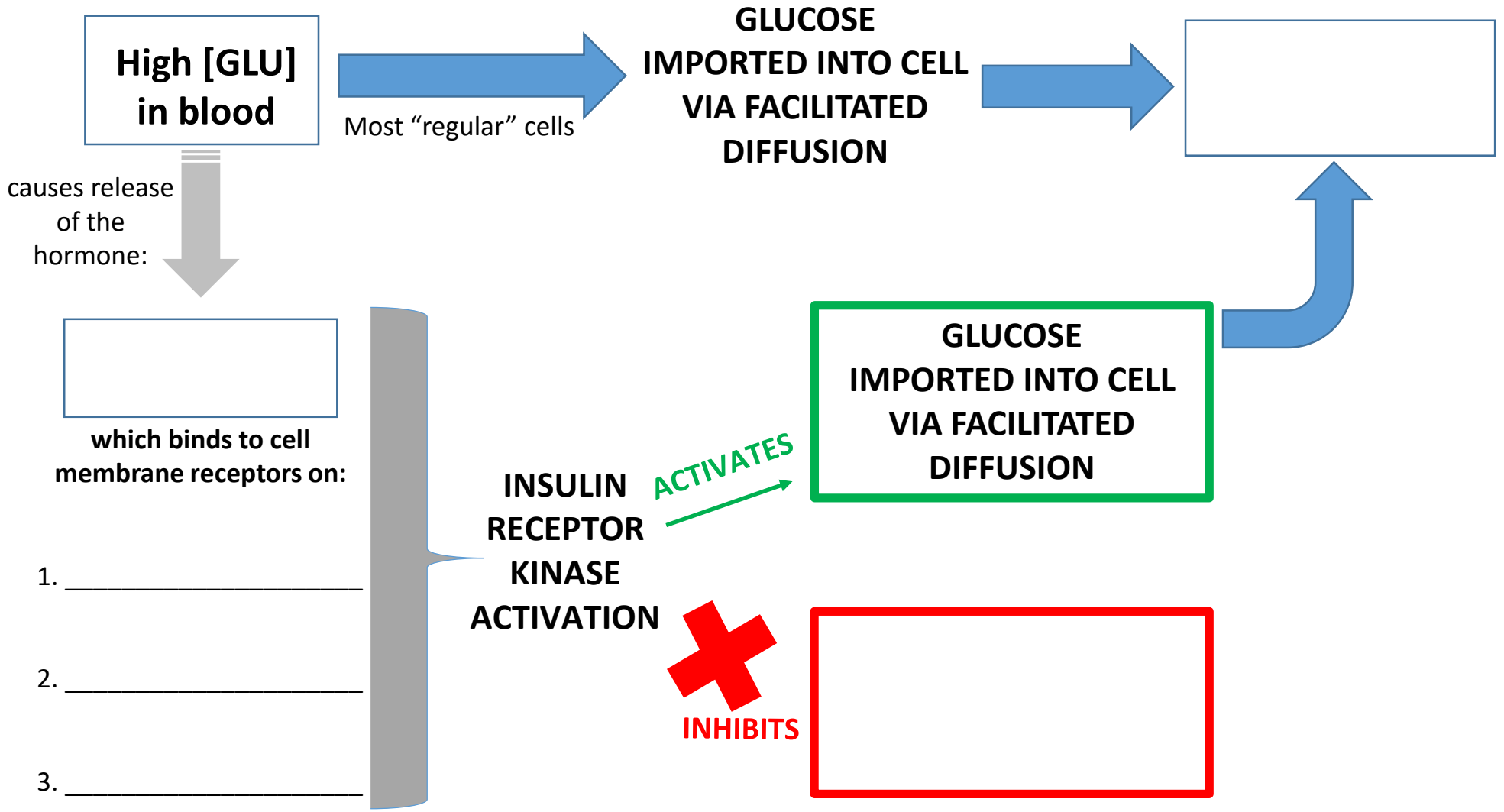
  1. Glucose transporter gene (*GLUT4*) activation in these cells
  glut4 gene activated → *glut4* mRNA → GLUT4 protein expressed on these cell membranes

  2. Glucose uptaken by GLUT4 and used in glycolysis
  (or storage into the polysaccharide Glycogen by Liver and Skeletal Muscle)

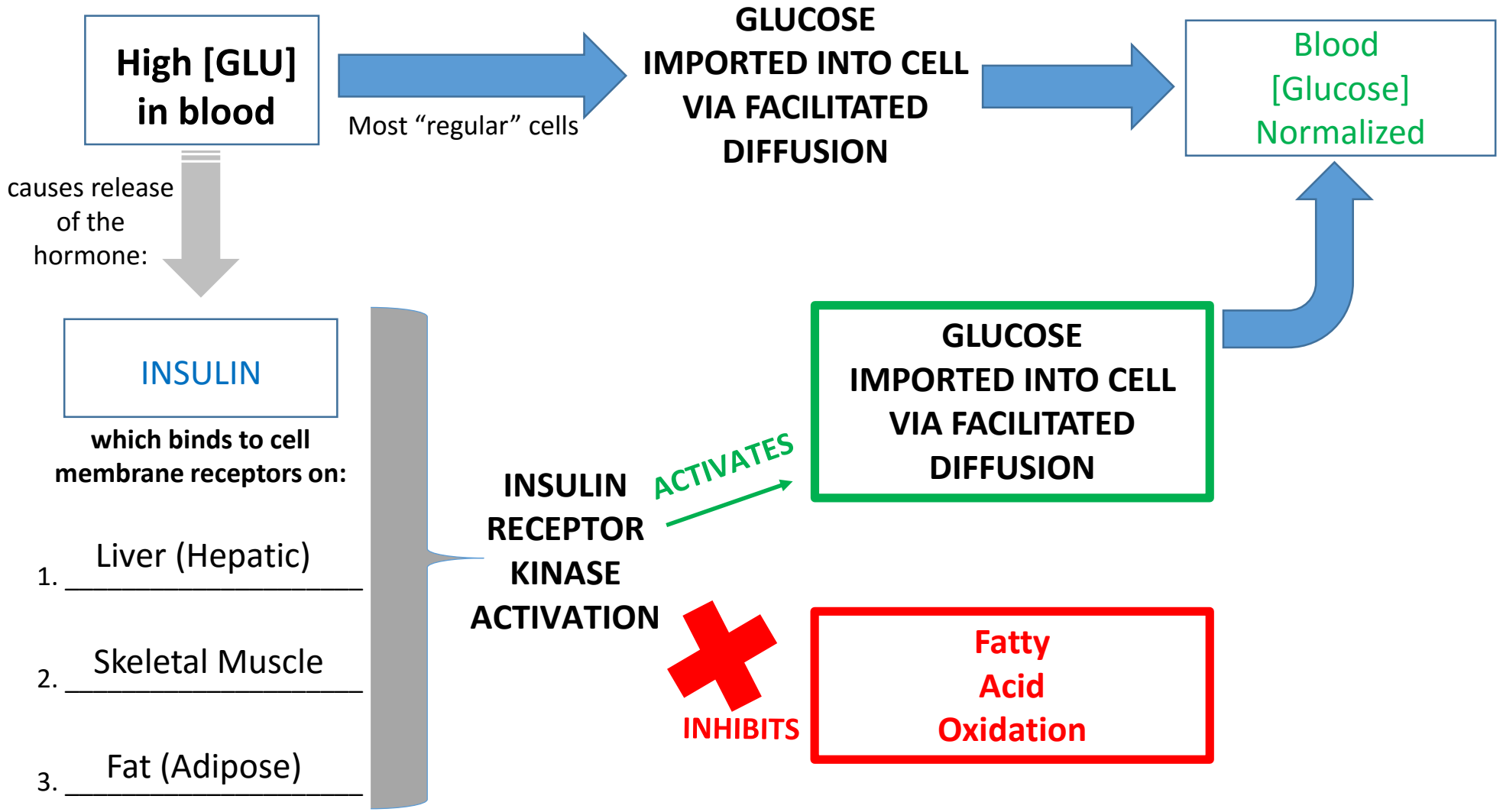
  3. Fatty acid oxidation enzymes repressed

  → Glucose used preferentially by all cells! Evolutionarily, humans try to use fat and protein reservoirs last!

NORMAL INDIVIDUAL



NORMAL INDIVIDUAL



Diabetic Individual

- Type I Diabetes is a genetic condition caused by a lack of proper beta-cell insulin secretion
- Type II Diabetes is an often-obesity related condition in which insulin is produced in response to high blood sugar, however, the insulin does not properly signal with Insulin Receptors (IR).
- In either of these situations, IR activation does not occur as it should in a diabetic.
- Lack of insulin signaling in diabetics causes the liver, skeletal muscle, and fat tissue to not import glucose and to rely heavily then on fatty acid oxidation.

Diabetic Individual

- Lack of glucose import into liver, skeletal muscle, and fat tissues results in an overall increase in blood and tissue glucose concentrations (as those 3 cell types are quite numerous in individuals)
- Glucose accumulation in the blood and tissues tends to “crystallize” causing dire effects in an individual
  - Increase in glucose outside of cells osmotically attracts intracellular water in cells → EDEMA (glaucoma, increase in overall fluid load in renal system → increase in urination and increase in overall thirst)
  - Increase in blood glucose “crystals” occludes small vessels in the body, doing damage over time (decreased circulation, damage to: kidney, retina, brain, reproductive organs)
  - Increase in tissue glucose “crystals” impairs cell to cell communication → nerve pain, decrease in immunological responses
  - Increase in overall glucose concentrations → increase in infections (as microorganisms thrive on the glucose!)

Diabetic Individual

- Increase in fatty acid oxidation/lack of glucose metabolism in liver, skeletal muscle, and fat tissue causes dramatic biochemical changes:
  - Increase in fatty acid oxidation → Increase in Acetyl-co A (point of entry of fatty acids in cellular metabolism)
  - In a diabetic liver, skeletal muscle, or fat cell, the Acetyl-co A builds up but cannot enter the CAC
  - Normally, Acetyl-coA is enters the CAC by covalently reacting with Oxaloacetate → Citrate
  - Oxaloacetate is derived from glucose entering into the cell, so if glucose cannot enter these cells, the CAC halts!
  - Because the CAC has stopped/decreased, the concentration of Acetyl-coA builds up in these cells
  - The Acetyl-coAs spontaneously dimerize in these cells → Acetoacetate (ketone body and H+ donor) which then further breaks down into Hydroxybuturate (another ketone body and H+ donor) and/or Acetone (ketone body that is not a H+ donor but can be detected as a “sweet smell”)
  - The H+ donor ketone bodies cause an increase in [H+] and decrease the overall pH of the body → ketoacidosis (which can lead to ketoacidosis shock and death)
  - Ketone bodies can be used by the brain for ATP production and are also formed in health individuals consuming a lipid-rich diet and have neuroprotective qualities.

DIABETIC INDIVIDUAL

1. _____
2. _____
3. _____

High [GLU] in blood

Most "regular" cells

GLUCOSE IMPORTED INTO CELL VIA FACILITATED DIFFUSION

"crystallizes" in tissues

INCREASED <u>TISSUE</u> GLUCOSE

GLUCOSE <u>NOT</u> IMPORTED INTO CELL

cellular osmosis influenced by [glucose]

THIRST!

INC. URIINE

INCREASED <u>BLOOD</u> GLUCOSE

"crystallizes" in blood vessels

POOR CIRCULATION IN KIDNEY, RETINA, BRAIN AMONG OTHER PLACES

TYPE I: <u>NO</u> INSULIN SECRETED

TYPE II: INSULIN <u>NOT</u> COMMUNICATING WITH:

1. _____
2. _____
3. _____

<u>NO</u> INSULIN RECEPTOR KINASE ACTIVATION

ACTIVATES

DIABETIC INDIVIDUAL

High [GLU] in blood

Most "regular" cells

GLUCOSE IMPORTED INTO CELL VIA FACILITATED DIFFUSION

TYPE I: NO INSULIN SECRETED

TYPE II: INSULIN NOT COMMUNICATING WITH:

1. Liver (Hepatic)
2. Skeletal Muscle
3. Fat (Adipose)

NO INSULIN RECEPTOR KINASE ACTIVATION

GLUCOSE NOT IMPORTED INTO CELL

ACTIVATES

Fatty Acid Oxidation

INCREASED TISSUE GLUCOSE

"crystallizes" in tissues

1. Nerve pain
2. Glaucoma
3. Increased infection/poor wound healing

INCREASED BLOOD GLUCOSE

"crystallizes" in blood vessels

POOR CIRCULATION IN KIDNEY, RETINA, BRAIN AMONG OTHER PLACES

cellular osmosis influenced by [glucose]

EDEMA

THIRST!

INC. URIINE

INCREASES

2-C molecule

KETONE BODIES*

Dimerized 2-C molecules

H+ donor

H+ donor

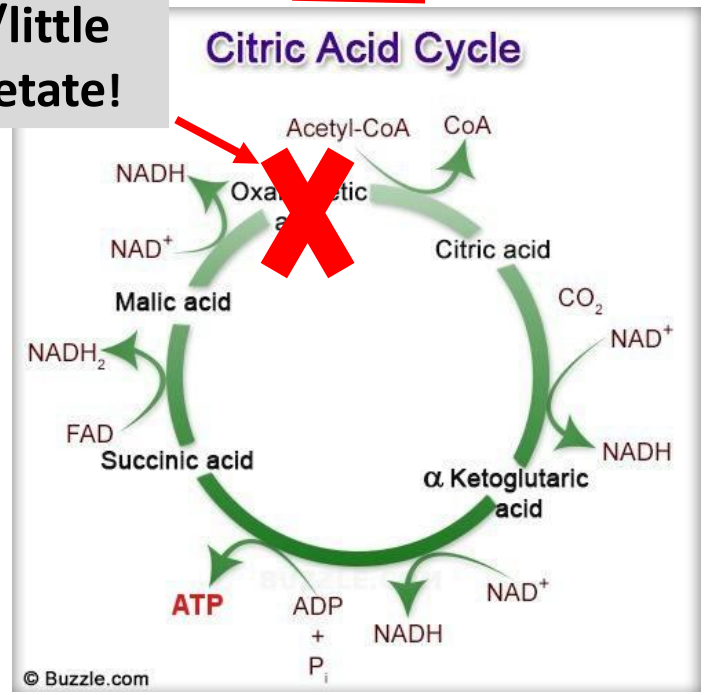
NOT H+ donor

"sweet smelling breath"

KETOACIDOSIS:

Blood pH lowers < 7.3

Due to low [GLU] in the cell, no/little Oxaloacetate!



KETONE BODIES can be used By brain for → ATP when fat is Being relied upon for ATP

*Seem to also have neuroprotective qualities

INCREASES [Acetyl-coA]

2-C molecule

KETONE BODIES*

Acetoacetate

Dimerized 2-C molecules H+ donor

Hydroxy-butyrate

H+ donor

Acetone

NOT H+ donor

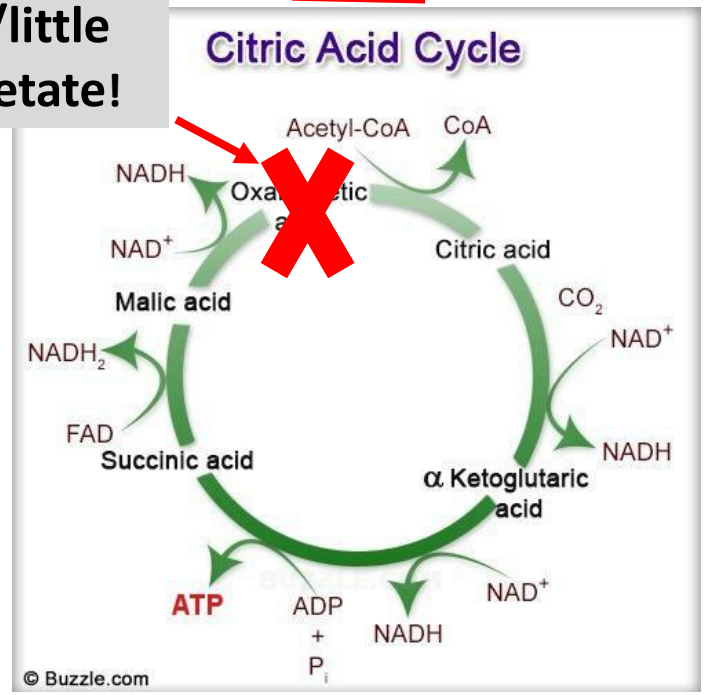
"sweet smelling breath"

KETOACIDOSIS:

Blood pH lowers < 7.3

Due to low [GLU] in the cell, no/little Oxaloacetate!

Citric Acid Cycle STOPS!



KETONE BODIES can be used By brain for → ATP when fat is Being relied upon for ATP

*Seem to also have neuroprotective qualities

References

- Gasior, Maciej, Michael A. Rogawski, and Adam L. Hartman. "Neuroprotective and disease-modifying effects of the ketogenic diet." Behavioural pharmacology 17.5-6 (2006): 431.
- Lehninger, Albert, *et al*. Principles of Biochemistry, 2005.
- Lodish, Harvey, *et al*. Molecular Cell Biology, 2012.