

## GLUCOSE METABOLISM IN WELLNESS AND DISEASE

### PHILOSOPHICAL CONTEXT

- State of the Organism (internal and External Environments)
- Over Fed + Under Exercised = Diabetic State

### BLOOD GLUCOSE (AKA BLOOD SUGAR)

- **Expected Value** = Between **70 mg/dL** (3.9 mmol/L) and **100 mg/dL** (5.6 mmol/L)
- **Monitoring Required:** Between **100 to 125 mg/dL** (5.6 to 6.9 mmol/L)
  - Lifestyle changes recommended
- **Diabetes:** **≥126 mg/dL** (7 mmol/L) on two separate tests
- **Too Low:** **< 70 mg/dL** (3.9 mmol/L)
  - dizziness, sweating, palpitations, blurred vision
- **Total Blood Glucose = 3.5-5.0 grams**

### GLUCOSE TOLERANCE TEST

- At fasting blood glucose – give 75 grams of glucose (oral)
- Monitor for 2 hours
  - <140 mg/dL = normal
  - 140-199 mg/dL = impaired
  - >200 mg/dL = diabetes
- Glucose peak >30 mins was associated with a **4-fold increased odds of prediabetes**

### GLUCOSE

#### BASAL METABOLIC CALORIC (CARBS/FAT/PROTEIN) REQUIREMENTS/USE

- Skeletal Muscle - 14.5 kcal/kg/day
- Heart - 440 kcal/kg/day
- Kidney - 440 kcal/kg/day
- **Brain - 240 kcal/kg/day (~must be glucose)** This equals about **400kcal/day of glucose**
- Liver - 200 kcal/kg/day

#### SKELETAL MUSCLE GLUCOSE USE (EXAMPLE: LEGS)

Resting <5 kcal/hour

Moderate Exercise = **100 – 150 kcal/hour**

Hard Exercise = **200 – 300 kcal/hour**

Hargreaves, M., & Spriet, L. L. (2020). Skeletal muscle energy metabolism during exercise. *Nature metabolism*, 2(9), 817-828.

#### Resistance Exercise (Lifting Weights) burns glycogen

- 8 sets – 10 representatives = ↓23% Slow Twitch Glycogen --- ↓42% Fast Twitch Glycogen (Koopman, et al. 2006)

## **INACTIVE MUSCLE CONSUMES VERY LITTLE GLUCOSE!**

### **SKELETAL MUSCLE GLUCOSE CAPACITY**

Untrained: **80 – 85 mmol/kg of muscle**

Trained = **120 mmol/kg wet weight**

Skeletal muscle glycogen stores = **300 – 700 grams**

Burke, L. M., van Loon, L. J., & Hawley, J. A. (2017). Postexercise muscle glycogen resynthesis in humans. *Journal of applied physiology*.

**\*\*\*A bigger, trained muscle holds much more carbohydrate** (glycogen). Small, untrained muscle is a much poorer consumer of carbohydrates.

### **GLUCOSE TRANSPORTERS (GLUTS)**

Glucose enters Liver, Muscle, and Pancreas via “facilitated diffusion”

Intermembrane transporters (GLUTs) facilitate transport from outside to inside the cell

#### **GLUT2**

- Tissues (**LIVER** and **PANCREAS**)
- **Low Affinity**
- **High Capacity**
- Cell Membrane (no translocation needed)

#### **GLUT4**

- Tissues (**SKELETAL MUSCLE** and **FAT**)
- **High Affinity**
- **Translocation** (it is activated by moving it from the cytosol to the membrane)
  - AMP
  - Insulin

### **ENZYMES**

#### **HEXOKINASE (SKELETAL MUSCLE)**

- Low  $K_m$  (runs fast at low concentrations)
- Inhibited by its product (G6P)
  - It will run very fast, even at low glucose levels, provided the cell is using its product

#### **GLUCOKINASE (LIVER)**

- High  $K_m$  (runs slowly at low concentrations)
- **Regulatory Protein** (Inhibits the enzyme)
  - Keeps it sequestered in the nucleus and inactive
  - Freed by high glucose and **fructose**
- NOT Inhibited by its product (G6P)

**LOCKED IN THE NUCLEUS!**

### **LIVER IS THE “CONTROLLER” OF BLOOD GLUCOSE**

- The liver gets blood glucose back down whenever it goes higher

- Runs fast whenever blood glucose is high
- Regulatory protein inhibits whenever blood glucose is low

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## GLUCOKINASE (PANCREAS)

- High  $K_m$  (runs slowly at low concentrations)
- **NO Regulatory Protein (No inhibition!)**
- NOT Inhibited by its product (G6P)

### *PANCREAS IS THE "SENSER" OF BLOOD GLUCOSE*

- Beta cells make and secrete insulin when intracellular ATP is high
- Lots of glucose coming into the Beta cell causes glycolysis to run fast and produces lots of ATP
- **High Glucose = High Beta Cell ATP = more insulin production and secretion**

## INTESTINE

- Multiple Glucose Transporters
  - **SGLT**
    - **Active Transport**
    - **Limited capacity**
  - **GLUT1**
  - **GLUT2**
    - **Recruited to the apical membrane**
    - **Very high capacity**
    - **Inducible**
  - Paracellular Transport

**It has a very large capacity to absorb whatever glucose you eat!**

## LIVER

- Receives portal circulation
- Retains 30-60% of glucose coming from portal circulation
  - Depends on:
    - **Glucose** concentration
    - **Fructose** concentration
    - **Insulin** concentration
- **GLUT2**
  - Half speed at **300 mg/dL**, but high capacity to take glucose
- **Glucokinase**
  - Half speed at **150 mg/dL**
  - Stimulated by fructose and glucose
  - Expression increased by insulin
  - NOT inhibited by G6P
  -

## THE LIVER MAKES FAT AND CHOLESTEROL OUT OF EXCESS GLUCOSE

- ✓ If ATP is high;
- ✓ If glycogen is full;
- ✓ Glucose turns into **fat** and cholesterol

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## INFLAMMATION

- **High fat production** with high insulin leads to:
  - More Diacylglycerol (DAG)
  - More ceramide production
  - Translocation/activation of protein kinase C (PKC)
    - Stimulation of inflammatory pathways (NFKB)

## PANCREAS

- Receives blood after the liver (systemic circulation)
- **GLUT2**
  - Half speed at **300 mg/dL**, but high capacity to take glucose
- **Glucokinase**
  - Half speed at **150 mg/dL**
  - NOT inhibited by G6P

## PANCREAS IS THE "SENER" OF BLOOD GLUCOSE

Beta cells make and secrete insulin when intracellular ATP is high

Lots of glucose coming into the Beta cell causes glycolysis to run fast and produces lots of ATP

- **High Glucose = High Beta Cell ATP = more insulin production and secretion**

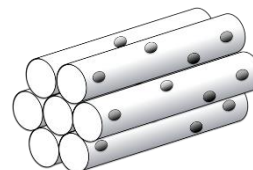
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## INSULIN

- Peptide hormone release from the **Beta cells** of the pancreas
- PI3K pathway
- MAPK pathway
- Stimulates liver glucokinase
- Stimulates **translocation of GLUT4**
  - Skeletal Muscle
  - Adipocytes
- Stimulates mTORC1
  - Transcription and translation of certain proteins

## SKELETAL MUSCLE

- Stores 300-700 grams of glucose (glycogen)
- Overnight fast – minimal impact
- Trained muscle can store 50% more glycogen (same volume)
- Adding muscle = adding storage capacity
- Resting muscle burns next to nothing
- Working muscle burns lots of glucose (**30-60 times more than resting!**)
- Muscle takes in lots of glucose after exercise (rebuild storage)



## GLUCOSE TRANSPORTER (GLUT4)

- 90% inside the cell at rest
- Activated (brought to the cell membrane) via
  - Insulin
  - Muscle contraction (AMP and Calcium)



### Insulin results in a 10-20-fold increase in muscle glucose uptake

Post-exercise insulin sensitivity ↑35-fold

### Exercise results in a 100-fold increase in muscle glucose uptake

## GLYCOGEN REPLETION

- **Rapid Insulin Independent**
  - 30-60 minutes after intense exercise
  - Low glycogen levels AND lots of GLUT4 in the membrane
- **Slower Insulin Dependent**
  - Several hours after exercise (insulin and carbohydrate present)
- **Maximal Resynthesis Rates**
  - ~300-500 kcal of carbohydrate per meal

- Maximal activity during the **first 30 minutes**
- Rapid decline to about **one fifth by 60 minutes**
- Reduced to about **one ninth by 120 minutes**

## ENZYME (HEXOKINASE II)

- Predominant form in muscle
- Very low  $K_m$  (runs even when glucose concentration is low)
- Moves between the cytosol and mitochondria
  - Drives glycolysis when membrane-bound
- **Insulin sensitive**
- $Mg^{++}$ ,  $Ca^{++}$  and **glucose deprivation** stimulate
- **Glucose 6P and  $P_i$  inhibit**

Wasserman, D. H. (2022). Insulin, muscle glucose uptake, and hexokinase: revisiting the road not taken. *Physiology*, 37(3), 115-127.

**Exercise results in muscle making more Hexokinase and GLUT4  
More Powerful Glucose Consumer!**

## FAT (ADIPOSE TISSUE)

- **Adipose Tissue** = adipocytes, pre-adipocytes, endothelial cells, vascular precursor cells, **immune cells**, and extracellular matrix
- **SWAT**: Subcutaneous White Adipose Tissue
- **VWAT**: Visceral White Adipose Tissue

## FAT STATS

- **Number** of subcutaneous white fat cells is **established around puberty**
  - turnover rate around 10%.
- Adipose tissue growth is **exclusively through hypertrophy**.

## ADIPOCYTE HYPERTROPHY

- **Bigger fat cells** kick out more Free Fatty Acids (FFA)
  - Oversupply of FFA leads to **lipotoxicity** in tissues
- **Bigger fat cells** secrete inflammatory cytokines
  - TNF alpha
  - IL-6
  - **Recruit and activate immune cells**
- **Bigger fat cells** die.
  - Fat cells reach a critical size → degenerate and die through pyroptosis.
  - Crown-Like-Structures (CLS)
  - **INFLAMMATION**
- **Bigger SWAT** divert fat to visceral white adipose tissue and ectopic sites

Hildebrandt, X., Ibrahim, M., & Peltzer, N. (2023). Cell death and inflammation during obesity: "Know my methods, WAT (son)". *Cell Death & Differentiation*, 30(2), 279-292.

## VISCERAL FAT AND INFLAMMATION

- **MACROPHAGE INVASION**
  - VWAT undergoes major cell death and inflammation
  - Adipocyte death causes a large influx of **MACROPHAGES**
  - **More** macrophages AND **more inflammatory** type macrophages
    - Macrophages switch (phenotype) from M2 to M1 (much more inflammatory)
      - Switch is specifically observed in VWAT.
      - Percent macrophages in the stromal vascular fraction goes from ~10% in lean to over 50% in obese individuals.

## ADIPOCYTE SENEESCENCE

Senescence is induced by various stress conditions

- Oxidative Stress - ROS (Reactive Oxygen Species)
- Metabolic Insults - **High glucose** and toxic lipids
  - (DAG – Ceramides)
- Visceral Adipocytes are more susceptible to senescence

Liu, Z., Wu, K. K., Jiang, X., Xu, A., & Cheng, K. K. (2020). The role of adipose tissue senescence in obesity-and ageing-related metabolic disorders. *Clinical science*, 134(2), 315-330.

**Hypertrophic Obesity → FFA Spillover into VWAT → FFA Spillover into Ectopic Sites**

## ADDITIONAL ONLINE CONTINUING EDUCATION (WEINERT)

- **INTERMITTENT FASTING**
- **GUT MICROBIOTA**
- **MUSCLE MATTERS**
- **GLUTEN AND CELIAC DISEASE**

<https://palmerce.learningexpressce.com/index.cfm?eventTypeID=0&categoryIDs=&q=weinert>

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