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/d**L (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

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

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

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

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

***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 Km (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 Km (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

GLUCOKINASE (PANCREAS)

- High Km (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*

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

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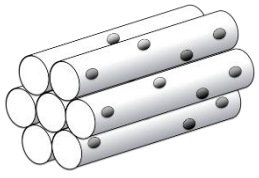
INSULIN

- 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 <u>hypertrophy</u>**.

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 SENESCENCE

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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