Outline

• What is metabolism and why should you care about it?
• Summary of human carbohydrate metabolism and connections to diabetes
• Metabolism in history and society: the twin “epidemics” of obesity and diabetes
• New approaches to understanding metabolic regulation in diabetes
Metabolism: You are what you eat

1. Extract components of biological macromolecules from food and rebuild into human tissues
2. Obtain energy stored in chemical bonds in food and convert into a useful form

Fat energy density = 9 kcal/g
2000 Calorie (kcal) per day diet = 0.5 lb of fat if stored
1 lb/year weight gain = 10 excess Calories (kcal) per day
Metabolic flux: molecular synthesis and degradation occur simultaneously

Biomolecules are constructed from a relatively small number of building blocks

Biosynthetic and degradative pathways for the same molecule tend to be segregated and reciprocally regulated

Flux through all pathways is remarkably balanced and adaptable
One typical reaction: phosphorylation of glucose (first step in glycolysis)

Hexokinase before binding glucose  Hexokinase with glucose bound; note change in lobes
Glycolysis
About 1/3 of protein domains conserved across all kingdoms are devoted to metabolism

| Information storage and processing                          | 217 | Translation, ribosomal structure and biogenesis |
|                                                              | 133 | Transcription                                   |
|                                                              | 184 | Replication, repair, recombination               |

534 total

| Cellular processes                                          | 32  | Cell division and chromosome partitioning       |
|                                                              | 109 | Posttranslational modification, protein turnover, chaperones |
|                                                              | 155 | Cell envelope biogenesis, outer membrane         |
|                                                              | 133 | Cell motility and secretion                      |
|                                                              | 160 | Inorganic ion transport and metabolism           |
|                                                              | 96  | Signal transduction mechanisms                   |

685 total

| Metabolism                                                  | 223 | Energy production and conversion                |
|                                                              | 170 | Carbohydrate metabolism and transport           |
|                                                              | 234 | Amino acid metabolism and transport             |
|                                                              | 85  | Nucleotide metabolism and transport             |
|                                                              | 154 | Coenzyme metabolism                             |
|                                                              | 75  | Lipid metabolism                                |
|                                                              | 64  | Secondary metabolites: biosynthesis, transport, and catabolism |

1005 total

| Poorly characterized                                       | 449 | General function prediction only                |
|                                                              | 753 | Function unknown                                |

1202 total
Energy release by controlled oxidation

(A) stepwise oxidation of sugar in cells

- SUGAR + O₂ → activated carrier molecules → CO₂ + H₂O
  - small activation energies overcome by body temperature

(B) direct burning of sugar

- SUGAR + O₂ → CO₂ + H₂O
  - large activation energy overcome by the heat from a fire
  - all free energy is released as heat; none is stored
Energy released by oxidation of food captured in activated carrier molecules

The metabolic web is driven by coupling of favorable reactions (e.g. ATP hydrolysis) to unfavorable reactions (e.g. synthesis of glucose-6-phosphate)

\[ A \rightarrow B + C \quad \Delta G = +5 \text{ kcal/mol} \]
\[ B \rightarrow D \quad \Delta G = -8 \text{ kcal/mol} \]
\[ A \rightarrow C + D \quad \Delta G = -3 \text{ kcal/mol} \]
Glycolysis and other modes of food oxidation generate ATP and NAD(P)H
Glycogen: high density storage form of glucose

Synthesized when blood sugar is high

Primarily made in liver and muscle tissue

Broken down when blood sugar is low

Glucose from liver glycogen can be released into bloodstream; muscle glycogen can only be used in the muscle

Polymer of glucose residues;

Compare starch and cellulose

Well-fed rat liver

Fasting rat liver
Gluconeogenesis converts lactate or alanine back into glucose

“Bypass enzymes” essentially allow reversal of “irreversible” steps in glycolysis
Requires net energy input
Enzymes required for gluconeogenesis are sequestered to prevent futile cycles
Expressed primarily in liver
Located in noncytoplasmic compartments (ER, mitochondria)
Regulated reciprocally with glycolytic enzymes (e.g. AMP activates glycolysis, inhibits gluconeogenesis)
Also regulated by hormones
Regulation of flux through metabolic pathways:

Availability of substrates
Concentration of enzymes
  Balance between synthesis (usually regulated at the level of transcription) and degradation (usually via ubiquitination)
Activity of enzymes
  Reversible allostERIC interactions
    When a pathway intermediate is an allostERIC effector for an enzyme in its own pathway, it will usually inhibit upstream enzymes (feedback inhibition) and activate downstream enzymes (feedforward activation)
  Reversible covalent modifications (e.g. phosphorylation; often due to hormonal regulation)
Key points of pathway regulation are the first committed step and any irreversible step (large negative $\Delta G$)
Insulin signals the well-fed state

Increases:
- glucose uptake by muscle and adipose tissue
- glycolysis
- glycogen synthesis
- triacylglycerol synthesis
- synthesis of DNA, RNA, protein

Decreases:
- gluconeogenesis
- glycogen breakdown
- fatty acid oxidation
- protein degradation
Regulation of blood sugar by the pancreatic “glucostat”

Glycolytic rate in pancreas and liver cells directly reflects blood glucose level
OTHER CELLS CANNOT MEASURE BLOOD GLUCOSE!

<table>
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<tr>
<th>Tissue distribution:</th>
<th>Hexokinase</th>
<th>Glucokinase</th>
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<tbody>
<tr>
<td>$K_m$</td>
<td>Most</td>
<td>Liver and $\beta$ cells</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>Low (0.1 mM)</td>
<td>High (10 mM)</td>
</tr>
<tr>
<td>Inhibition by G6P</td>
<td>Yes</td>
<td>No</td>
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</table>

Insulin also regulates glucose uptake in muscle and fat cells
Human metabolism is coordinately regulated among different organs

The well-fed state

The fasting state
Stages in glucose homeostasis

Diabetes: Tissues think that they are starving even though blood sugar remains high.
Chronic hyperglycemia causes severe diabetic complications

- Glucose excreted in urine, massive increase in urine production, dehydration
- Stress on kidneys can result in renal failure
- High blood pressure due to increase in blood osmolytes can lead to retinopathy
- Frequent fungal infections due to low pH environment
- Swelling of tissues that convert glucose into sorbitol, including lens and nerve, and microvascular pathologies resulting in peripheral neuropathies and retinal damage
- Non-enzymatic glycosylation of blood vessel lining promotes atherosclerosis, stroke, and cellulitis
- Hyperlipidemia
- Ketoacidosis (primarily in type I)

5 mM ~ 100 mg/dL
Consequences of diabetic hyperglycemia

Glycolytic pathway

- Osmotic stress
- Peripheral neuropathy
- Effects on endothelial cells
- Effects on blood flow, inflammation
- Buildup of glycosylated proteins in retinal blood vessels, kidney glomeruli

Brownlee, 2001, Nature 414: 813
Origins of diabetes

Type I: Destruction of insulin-producing pancreatic islet cells (often autoimmune, can be triggered by viral infection)

Type II: Related to overall metabolic state (positive feedback loop?) Insulin resistance usually precedes beta cell dysfunction

![Graph showing glucose levels and insulin resistance over time]
“Metabolic syndrome”

Prevalence: Up to 25% of US adults

Considered to be a strong predictor of Type II diabetes
Metabolism in human history

50,000 years:
Food was scarce and seasonal, famines were frequent
Metabolic adaptations for efficient storage enabled survival

100 years:
Food is abundant in many societies, year-round
Consequence: WIDESPREAD METABOLIC DISORDERS
...including obesity and type 2 diabetes

An extreme case: The Pima people, southern Arizona
Caucasians in the American Southwest:
6% have type 2 diabetes, average age of onset 60

Pimas in the American Southwest:
60% have type 2 diabetes, average age of onset 36

Ongoing longitudinal studies with NIH since 1963:
Flux balance gives steady-state body mass

\[ BMI = \text{body mass index (kg/m}^2\text{)} \]

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<tr>
<th>Underweight</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
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<td>Source: Nutrition Project, Stanford University Medical School, 2000</td>
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Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

1990
1998
2007

www.cdc.gov
Medical consequences of obesity

Note these are CORRELATIONS, not proof of causation
But, if obesity were causative, these numbers predict that a
US population with BMI <25 would reduce:
- Coronary heart disease by 25%
- Strokes and congestive heart failure by 35%
- Type II diabetes by 70%

Women: RR is 18.1 for BMI ≥ 31
Men: RR is 50.7 for BMI ≥ 35
Obesity epidemic largely caused by changes in environment, activity

Eat more:
Increased food availability
- Calories/person/day has increased 15% since 1970
- $ spent on food outside the home has doubled since 1970
Increased portion size
- 12 oz. Coke at McDonald’s: king-size in 1950’s, child-size now
Increased energy density (kcal/gm)
- High fat foods, low fat/low cal foods

Do less:
Increased sedentary leisure time activities
- TV, video games, computers
Decreased occupational physical activity
Increased use of automobiles

News Flash:
Cookie Monster to eat fewer cookies, more fruit

[[Image of Cookie Monster]]

CDC

Prevalence of childhood obesity

[Graph showing prevalence of childhood obesity from NHANES surveys 1971-1974 to 2003-2006]
BUT: Obesity is not the only contributing factor for Type II diabetes

Many overweight people are not diabetic
Many diabetics are not overweight
How can we find the other genetic and environmental factors?

Genetic variation contributes to metabolic differences

Predictive value may be low, but genetic variations associated with increased risk can point the way toward new drug targets, etc.

CANDIDATE GENES:
Example: Leptin knockout mouse
Peptide secreted by adipose tissue, signals satiety
Note most obese people have normal or increased leptin levels; tissues are leptin resistant

Alternative approach, GENOME-WIDE ASSOCIATION: examine human variations and find correlations with obesity and type II diabetes
Rate of identification of new genes is accelerating…

Most risk effects are modest

Interactions are unknown

Many genes are associated with beta-cell function rather than insulin resistance

What can we do with this knowledge?


Challenges: Diabetes is a complex, chronic metabolic imbalance

Metabolic flux in a human is HUGE and RAPID: imbalances are very, very small for syndromes that unfold over years

Individual genetic variation can produce different outcomes for the same environment

Environmental variation can produce different outcomes for the same genetic background
Knowledge of genes and risk factors is incomplete; interactions are complex

New approaches to prevention and treatment must rely on interdisciplinary research... what will you do?