Integration & Hormone Regulation

Integration
Branchpoints in metabolism where metabolites can go several directions

1. Glucose 6-phosphate
Energy needed (low energy charge): glycolysis
Low blood sugar: high [glucagon], low [insulin]
   glycogen synthesis turned OFF via glycogen synthase
   glycogen breakdown turned ON via phosphorylase
In liver: G6P converted to Glc and exported via glc 6 phosphatase

After meal: high energy charge turns glycolysis off
High blood sugar: low [glucagon], high [insulin]
   glycogen synthesis turned ON
   glycogen breakdown turned OFF
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2. **Pyruvate**
Aerobic conditions, need energy:
- Dehydrogenate to acetyl CoA
- Pyruvate dehydrogenase active b/c:
  - [NADH] low (Ox phos active)
  - [acetyl CoA] low (TCA active)
When NADH and acetyl CoA low, pyr dehydrogenase unphosphorylated b/c kinase inactive so PDH ACTIVE!
When NADH and acetyl CoA are high, stimulate kinase that phosphorylates PDH so PDH INACTIVE!

Anaerobic conditions, need energy:
- Reduce pyruvate to lactate
- No O₂, so no ox. Phos.
- NADH, FADH₂ accumulate
- [NAD⁺], [FAD] low in mito So TCA STOPS!
- Acetyl CoA accumulates
When NADH and acetyl CoA are high, stimulate kinase that phosphorylates PDH so PDH INACTIVE!
- Pyruvate diverted to lactate dehyd. when PDH inactive
- Recovers NAD⁺ for further glycolysis
- Lactate sent to liver to reconvert to pyruvate
Need TCA intermediates or glc
- Carboxylate pyruvate to oxaloacetate
- High [acetyl CoA] activates pyr carboxylase, inactivates PDH
High energy charge: TCA OFF, gluconeogenesis ON (OAA)
- Low energy charge: gluconeogenesis OFF, use OAA for TCA
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3. Acetyl CoA

Aerobic conditions, need energy:
- send to TCA (presence of O$_2$ signaled by FAD and NAD$^+$
- Make lots ATP

No carbs, need energy:
- Acetyl CoA comes from β oxidation
- Cannot synthesize carbs from fat
- TCA not functioning (intermeds drained off, not replaced) SO acetyl CoA diverted to ketone body synthesis

No energy needed:
- No ADP around (all in form of ATP)
- Ox phos stops
- NADH, FADH$_2$ accumulate, so NAD$^+$ and FAD low
- TCA stops
- FA biosynthesis turned on by hormones signaling fed state
- acetyl CoA diverted to FA biosynthesis

Cholesterol low:
- HMG CoA reductase levels high, cholesterol made
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Organ specialization

1. Brain
No glycogen or stored fat.
Totally dependent on oxidation of blood glucose

High energy demand:
   2% of mass of body
   uses 20% of O$_2$ consumed
   Much energy use due to (Na$^+$-K$^+$)-ATPase

Irreversibly damaged if [glc] drops by >50%
Blood-brain barrier: no uptake of FA
Starvation: brain adapts to use of ketones
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Organ specialization

2. Muscle
Skeletal muscle:
   Rested, fed muscle is 1-2% glycogen by mass
   Glycogen rapidly converted to G6P for energy
   Lacks G6Ptase, so glc is not exported, must be used in muscle
   Rapid bursts of activity fueled by fermentation to lactate
      (acid pH causes muscle fatigue)
   Cori cycle: lactate exported via blood to liver, liver
      reconverts lactate to glc, glc sent back to muscle
   In resting muscle, glycogen synthesized not used
   Energy from oxidation

Heart muscle:
   Work load pretty constant
   Metabolism solely aerobic (40% volume of cell = mito)
   Very low glycogen stores
   Depends on constant supply of O₂ and fuel
   Fuel = FA, glc, ketones, lactate
3. Adipose tissue
Stores huge energy reserves: triacylglycerols
Exports FA to blood when fuel needed
Two signals of need for fuel integrated:

• Hormones (glucagon, epinephrine, insulin) regulate lipases that release FA
Organ specialization

4. Liver
Maintains proper levels of nutrients in blood for use by brain, muscles, etc.
Dietary nutrients pass through liver first
Liver absorbs or releases stored nutrients as necessary
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Organ specialization
4. Liver
Liver as a glucose buffer

Blood glucose
= ~6 mM after meal
Brain damage
= <2 mM [glucose]

Muscle & fat cells

Hexokinase
$K_M=0.1$ mM
(G 6-phosphatase absent)

Glucose

Uptake stimulated by insulin

Glucose

G 6-P

Pyruvate
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Organ specialization

4. Liver
Liver as a glucose buffer

Fed state:
- Hormones allow FA biosynthesis in liver
- $\beta$ oxidation blocked (malonyl CoA (FA biosyn intermed.
  blocks carnitine acyltransferase: no FA enter mito)
- FA synthesized in liver or absorbed by liver from diet,
  exported as VLDL to adipose tissue)

Fasted state:
- Hormones block FA synthesis in liver
- FA from adipose enters liver
- FA enters mito, $\beta$ oxidation converts to acetyl CoA
- TCA turned OFF due to lack of intermeds
- Acetyl CoA converted to ketones, exported to blood for use
  by brain
Glucagon: signals fasted state, mobilizes stored glycogen & fat, receptors on liver & fat cells
↑ glycogen breakdown (↑ glyc phos), ↓ glyc syn (↓ glyc synthase), in liver lowers F26BP, ↓ glycolysis, ↑ gluconeogenesis, in fat cells ↑ lipases, releasing FA and glycerol

Insulin: signals fed state, stops utilization of stored glycogen & fat and ↑ synthesis
↑ glyc syn (↑ glyc synthase, ↓ glyc pho), ↑ glucose transporters on muscle and fat cells (muscle makes glyc, fat make FA
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What regulates regulators?

Neuroendocrine origins of signals

Central nervous system

Hypothalamus

Hypothalamic hormones (releasing factors)

Anterior pituitary

Posterior pituitary

First targets

- Corticotropin (ACTH) $M_r 4,500$
- Thyrotropin $M_r 28,000$
- Follicle-stimulating hormone $M_r 24,000$
- Luteinizing hormone $M_r 20,500$
- Somatotropin (growth hormone) $M_r 15,000$
- Prolactin $M_r 22,000$
- Oxytocin $M_r 1,007$
- Vasopressin (antidiuretic hormone) $M_r 1,040$
- Blood glucose level

Second targets

- Adrenal cortex
  - Cortisol, corticosterone, aldosterone
- Thyroid
  - Thyroxine $T_4$, triiodothyronine $T_3$
- Ovaries/testes
  - Progesterone, estradiol, testosterone

Ultimate targets

- Many tissues
- Muscles, liver
- Reproductive organs
- Liver, bones
- Mammary glands
- Smooth muscle, mammary glands
- Arterioles
- Liver, muscles
- Liver, muscles, heart

Sensory input from environment
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**Leptin story**

- Signals fed
- Curtails appetite
- Protein product of OB gene
Leptin story

Defective OB gene
Constant state of starvation
No leptin given

Other metabolic probs
similar to Type II diabetics
(resistance to insulin)

Defective OB gene
Leptin given