Overall Energy metabolism: Integration and Regulation

We have discussed various fuels which are oxidized via different catabolic pathways to generate ATP, or reducing equivalents required to carry out various functions and synthesis.

Fuels sources:
- Starch/Glycogen
- Glucose
- Fat or triacylglycerol
- Fatty acids and Glycerol
- Proteins
- Amino acids

Catabolic pathways:
- Glycolysis
- PDC and Citric Acid Cycle
- Oxidative phosphorylation
- Fatty acid Oxidation
- Amino acid catabolism = ammonia + carbon skeleton

Metabolic fate of different fuel sources in mammalian systems

Glucose as a central player in metabolic pathways in biological systems

Organ specialization for metabolic activity:
When we look at the whole picture of metabolic activity and its regulation in our body, it is an amazingly beautiful, well organized and the most complex and well-coordinated system.

First we look at what each major organ in body is specialized for:

Liver:
- It is the chemistry capital of the body. It is capable of catabolism as well as anabolism (synthesis) of any of the aforementioned fuel sources i.e glucose, fat and amino acids.
- It is responsible for maintaining proper glucose concentration in the circulation, managing the storage and distribution of excess fuel intake, synthesis of glucose from non-carbohydrate precursors (gluconeogenesis) in extreme conditions and detoxification of toxic waste such as ammonia.
- Liver has glycogen as emergency storage (10% of total liver mass, i.e. about 150 grams)
- Liver is also responsible for synthesis, and maintenance cholesterol in the body.

Metabolism of Fatty acids in liver
**Metabolism of Amino acids in liver**

**Metabolic pathway for Glucose 6-phosphate in the Liver**

**Muscle:**

- Major fuel for muscle are: Glycogen, glucose and Tryacylglycerol (fat) and ketone bodies. In extreme condition it can utilize amino acids.
- Remember the acetyl coenzyme A, and ketone bodies (both largely produced from fat catabolism) can be utilized only in aerobic condition.
- Muscle is capable of anaerobic catabolism of glucose generating a quick flux of energy by glycolysis and lactic fermentation.
- Lactate generated by homolactic fermentation during exercise causes decrease in the pH and leads to muscle fatigue.
- Muscle stores Phosphocreatine as emergency energy stock.
- Phosphocreatine + ADP = ATP + Creatine
- Lactate is transported to liver via blood where it is converted to glucose through gluconeogenesis, and glucose is transported back to muscle. This inter-organic metabolic pathway is referred as Cori cycle.
- Heart is largely aerobic.

**Energy source for skeletal muscle contraction**

- Skeletal Muscle contain 10-30 mM phosphocreatin as emergency source of energy. Creatin kinase can rapidly produce ATP from creatin phosphate a ADP.
- In relaxation phase, the reaction goes in other direction making creatin using ATP.

**Cori cycle: glucose-lactate cycle**

**Glucose-Alanine cycle**
The Brain

Brain is very active in oxidative phosphorylation.

It consumes 20% of total oxygen taken by whole body in resting stage. Remember brain is only 2% of the total body weight. Most of the ATP generated is used by Na⁺/K⁺ ATPases and other ion channels to maintain membrane potential needed for nerve impulse conduction (generation of action potential, and its transmission across the axons).

Preferred fuel: Glucose. In extreme situations it can use ketone bodies.

Catabolic Pathways: Glycolysis, citric acid cycle and oxidative phosphorylation.

Brain has very little or no glycogen storage, it depends entirely of the blood glucose which should be maintained at around 5 mM in blood. Lower level of glucose (less than 2.5 mM causes brain dysfunction, and coma.

Extended period of very low glucose (hypoglycemia) in blood may cause irreversible damage to brain or death.

Adipose tissue:

Adipose tissues are widely distributed throughout the body, prominently around abdominal cavity and upper part of limbs, thighs.

The function of adipose tissues: Store and release fatty acids as required by the body, provide insulation for temperature, protect from physical damage and butification.

These tissue obtain the fatty acids from circulation and store them as triacylglycerol.

Under hormonal influence they release fatty acids into circulation to be used by other tissues.

A 70 Kg person has about 15 Kg of fat, which is equivalent to 141000 Calories. Thus the normal fat storage is sufficient to meet body’s energy requirement for 3 months.
Fuel metabolism in liver during prolonged starvation

<table>
<thead>
<tr>
<th>Type of Fuel</th>
<th>Weight (g)</th>
<th>Caloric Equivalent (kcal/g)</th>
<th>Estimated Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal 70 kg man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmitoyl-CoA (adipose tissue)</td>
<td>25</td>
<td>141 (598)</td>
<td>1</td>
</tr>
<tr>
<td>Proteins (mainly muscle)</td>
<td>6</td>
<td>24 (1050)</td>
<td>15</td>
</tr>
<tr>
<td>Glucose (muscle, liver)</td>
<td>0.225</td>
<td>0.96 (3.8)</td>
<td>15</td>
</tr>
<tr>
<td>Gluconeogenesis, etc.</td>
<td>0.025</td>
<td>0.10 (0.42)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>166 (694)</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Obese 140 kg man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmitoyl-CoA (adipose tissue)</td>
<td>80</td>
<td>782 (3,143)</td>
<td>3</td>
</tr>
<tr>
<td>Proteins (mainly muscle)</td>
<td>9</td>
<td>32 (1343)</td>
<td></td>
</tr>
<tr>
<td>Glucose (muscle, liver)</td>
<td>0.23</td>
<td>0.90 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Gluconeogenesis, etc.</td>
<td>0.025</td>
<td>0.11 (0.48)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>785 (3,285)</td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.
In 1975, Dr. Saran Narang developed the synthetic primers technology that enabled the development of DNA cloning and later, DNA sequencing. Consequently, in 1982 he achieved the first total synthesis of proinsulin, an achievement for which he received the Order of Canada.

Nutritional calories: 1 Cal = 1 K calories = 4.1 KJ

Defined as total amount of energy released during complete oxidation of the food (i.e. Carbohydrate, fat or proteins).

Estimated by measuring the heat released during direct oxidation of the fuel (burning)

The total free energy for complete oxidation of 1 Mole of glucose (180 gm),

\[ \text{Glucose} + 6\text{O}_2 \rightarrow 6\text{CO}_2 + 6\text{H}_2\text{O} \quad \Delta G_{\text{oxy}} = -2840 \text{ kJ/mol} = -686 \text{ Cal} \]

Total amount of ATP generated = 32 moles (physiological number)

Total amount of free energy generated = 32 x 50 KJ = 1600 KJ = 382.77 Cal

The percentage of free energy stored in the form of chemical energy in ATP molecules is approximately 56%.

Rest is lost as heat.

One gram of Carbohydrate generates approximately = 3.74 Cal = 16.7 kJoules

One gram of fat = 9.3 Cal

These are total energy produced. Only 56% of this will be stored in ATP.
Alcohol Toxicity:

Two enzymes in liver catabolize alcohol consumed during drinking.

1. Alcohol dehydrogenase: converts Ethanol to acetaldehyde using NAD⁺ as oxidizing agent thus producing NADH.

\[ CH_3CH_2OH + NAD⁺ \rightarrow CH_3CHO + NADH + H⁺ \]

2. Aldehyde dehydrogenase: Oxidizes acetaldehyde to acetate using NAD⁺ thus producing NADH.

\[ CH_3CHO + NAD⁺ + H₂O \rightarrow CH₃COOH + NADH + H⁺ \]


Thus, there is accumulation of fatty acids that leads to the accumulation of fat in liver leading to hyperlipidemia or fatty liver.

Since CAC is inhibited, availability of oxaloacetate is also limited, this leads to the inhibition of gluconeogenesis leading to hypoglycemia.

Excess of NADH accelerates lactate dh to produce lactic acid leading to hyperlacticacidemia.

Accumulation of lactic acid, and acetic acid cause acidosis in liver.

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Reduced adiposity in bitter melon (Momordica charantia) fed rats is associated with lower tissue triglyceride and higher plasma catecholamines.

**Full Papers**


Chen, Qixuan; Li, Edmund T. S. *

Abstract:

Slower weight gain and less visceral fat had been observed when rats fed a high-fat diet were supplemented with freeze-dried bitter melon (BM) juice, the metabolic consequences and possible mechanism(s) were further explored in the present study. In a 4-week experiment, rats were fed a low-fat (70 g/kg) or a high-fat (300 g/kg) diet with or without BM (7.5 g/kg or 0.75%). BM-supplemented rats had lower energy efficiency, visceral fat mass, plasma glucose and hepatic triacylglycerol, but higher serum free fatty acids and plasma catecholamines. In the second experiment, 7-week BM supplementation in high-fat diet rats led to a lowering of hepatic triacylglycerol (P < 0.05) and steatosis score (P < 0.05) similar to those in rats fed a low-fat diet. BM supplementation did not affect serum and hepatic cholesterol. However, plasma epinephrine and serum free fatty acid concentrations were increased (P < 0.05) in the third experiment, BM7.5 and 15 g/kg) and 15% middle do51% BM lowered triacylglycerol concentration in red gastrocnemius and tibialis anterior (P < 0.05). These data suggest that chronic BM feeding leads to a general decrease in tissue fat accumulation and that such an effect is mediated in part by enhanced sympathetic activity and lipolysis. BM or its bioactive ingredient(s) could be used as a dietary adjunct in the control of body weight and blood glucose.
In 1994, obesity gene (OB/OB) was discovered, and a defect in obese gene caused obesity in mice.

This gene encodes a protein called leptin. Leptin is produced by adipocytes.

Injection of leptin in obese mice caused weight loss and loss of appetite in these mice.

Thus Leptin was shown to play a major role in fat catabolism.

But for human, there seem to be other complications.

Amino acid sequence of Neuropeptide Y

Decrease in the availability of leptin in brain leads to the secretion of neuropeptide Y from hypothalamus in brain. Neuropeptide Y stimulates appetite and promotes insulin secretion.

Structure of Human leptin as estimated by X-Ray crystallography.

Leptin is a 16 kDa protein normally produced by adipocytes.

In human obesity disorder, there is no deficiency of leptin production, but there might be defects with the leptin receptors in brain or problem with blood brain barrier which may limit the access of leptin to hypothalamus.

In near future we expect this mechanism to be exactly elucidated and we hope that there would be a solution to obesity very soon.
POMC = Pro-opiomelanocortin
MSH = Melanocyte stimulating hormone
CRH = Corticotropin releasing hormone
CART = Cocaine and amphetamine-regulated transcript