BCMB2X01

Biochemistry and Molecular Biology (II)

S1 2018

Table of Contents

Lecture 16 x Lecture 17: Cellular Metabolism, Energy Balance and Fuel Oxidation

In the context of fuel selection during exercise.

Muscle Cells

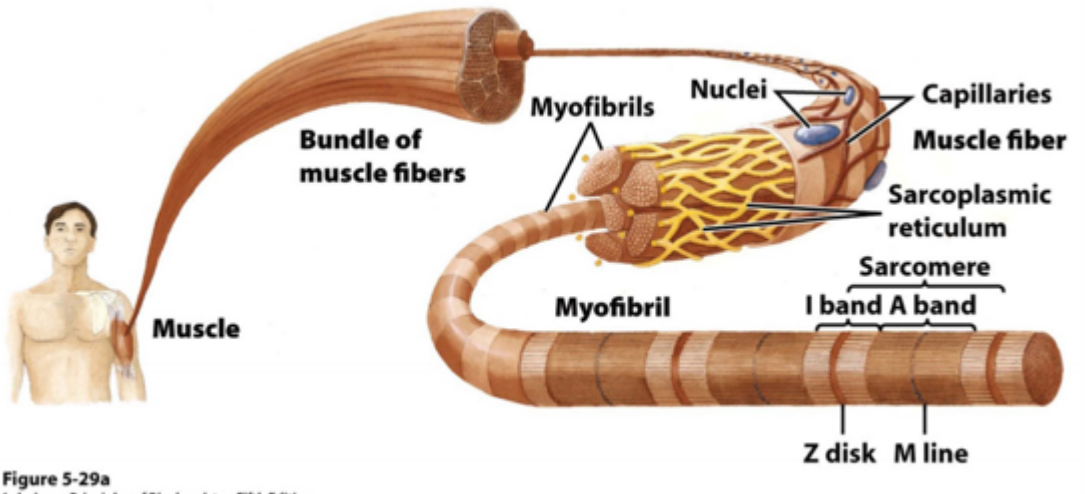

Figure 5-29a
Lehninger Principles of Biochemistry, Fifth Edition
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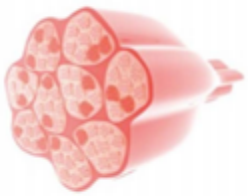
Sarcoplasmic reticulum – calcium continually pumped into the SR, making [Ca] high and very low in the muscle cell. Once nerve impulse is deliver to SR, all the Ca will be pumped into the cell, and then sliding of myosin, increasing ATP.

However, even when the muscle isn't being used, we are still consuming ATP to maintain that calcium gradient – and other activities to keep the cell alive.

Muscle Cell Types


RED MUSCLE
high mitochondrial content

1. Type I – "red", "slow"
    - Contracts relatively slowly
    - **Many mitochondria (what makes the cell red)**
    - **Good blood supply**
    - e.g. pectorial muscle for migrating birds


WHITE MUSCLE
low mitochondrial content

2. Type IIb – "white", "fast"
    - Contracts relatively rapidly
    - **Few mitochondria**
    - **Poor blood supply**
    - Packed full of contractile filaments (therefore low mitochondria and blood vessels – for power.
    - e.g. lobster tail

First Events

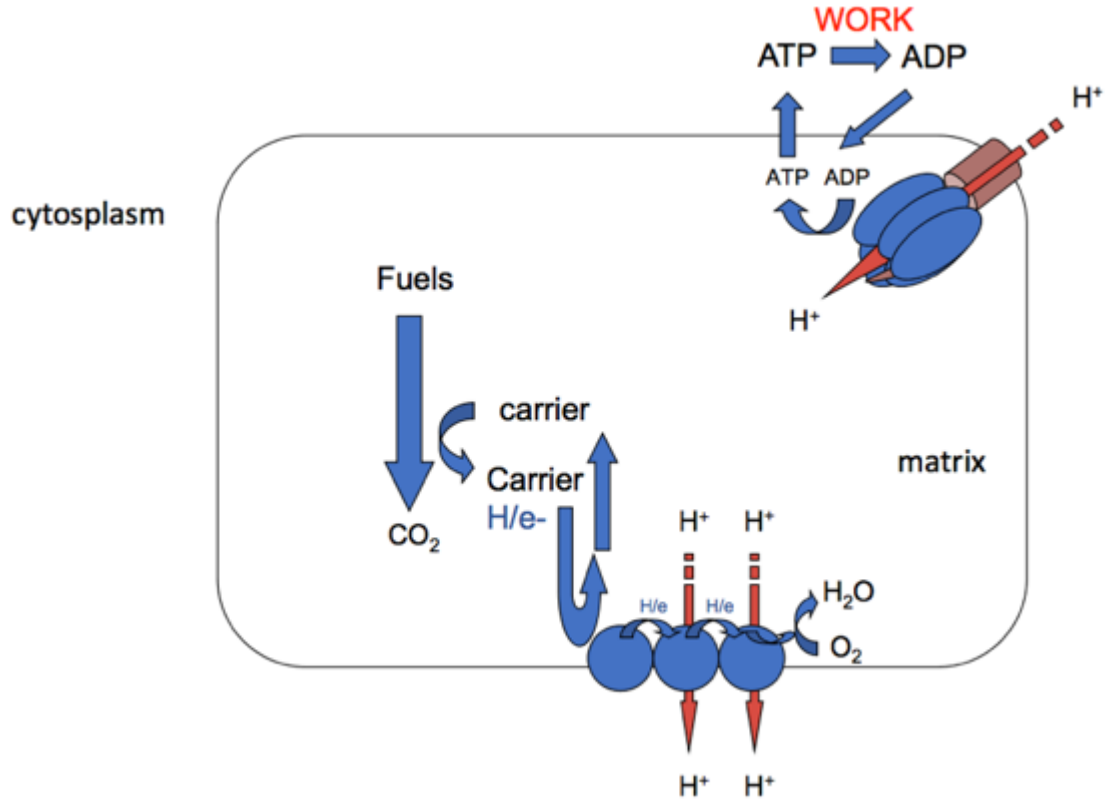
e.g. low intensity exercise.

We need a decent supply of ATP to keep the contractions going. But our stores of **ATP are low 5mM**, but during high intensity exercise we use 3mM per second, but if [ATP]<3mM, our cells die.

- Sprinting muscles use ATP at 5 µmol/g (5 mM) per second

- Increase in ATP consumption
  - What will be the *immediate* response at the molecular level?
    - We generate ATP in real time – muscles begin contracting and therefore the [ATP] will start to drop.
  - What are our stores of ATP like?
    - Very low
  - How can the cell maintain the level of ATP?
    - Generate ATP in real time
  - What happens if the ATP concentration drops too low? (what is too low?)
    - Cells die, <3mM

How fuel is used to make ATP



Note: Mitochondria, in the top right, is our ATP synthase – generates ATP – powered by protons gradient. Large [H+] enters into the ATP synthase via the F0 channel, in the process, squeezing together a molecule of phosphate with ADP to create ATP.

Because there is so much pressure and high concentration of protons on the outside, and so few in the matrix, it wants to push through into the matrix.

We create the high concentration of H+ via the electron transport chain (bottom) – pumps protons from the inside of the mitochondria to the outside.
The carriers will rip out the H+ and e- from the fuels and deliver it to the first carrier in the electron transport chain; process repeated – known as fuel oxidation.

- Carriers are in short supply.
- Only able to oxidize once the H+ and e- is delivered to the electron transport chain.

Note: what gets net used/produced and what is recycled? Protons, carriers, ADP
What is the overall formula? Fuel + oxygen → CO_2 + H_2O.

However, ADP is in short supply – [ADP] approx. 0.4mM – the availability therefore influences the efficiency of this process.

CONCEPT: a lot of the components in the process are in short supply e.g. H/e- carriers, ADP etc.

- ATP is really stable – it will stay as ATP until an enzyme directs it to hydrolyze, in this cause the actin myosin sliding (in making ATP, we have used up a ADP).

- The inner mitochondrial membrane is impermeable to protons – enters only through ATP synthase

- Protons only flow into the matrix if the ATP is being made

- The proton pumps don't work if the proton gradient is very high i.e. there is a maximal level, where the pumps can't pump out H+ into the gradient.

- No proton pumping, no H/e- movement down the ET chain

Coupling

i.e. every component of the process is intimately linked and cannot occur unless another component occurs.

**If we stop doing WORK → we no longer make ADP → no ADP for ATP synthase → no dissipation of proton gradient, reaching maximum → proton pumps stop working → movement of H+ and e- stops → carriers cannot oxidize fuel.

The lack of ADP every quickly stops the oxidizing of fuel; very sensitive to ADP created. Vice versa, if WORK increases, fuel oxidation immediately increases.

However, the only regulation occurs in the ATP synthase end, demand driven process i.e. the amount of WORK, rate in which we need ATP. Cells can't burn duel without doing work.

Note: ATP stores are pathetic; we have to generate it as it is being used.

- The rate of ATP synthesis, EXACTLY (to the nM) matched to the rate of ATP use.

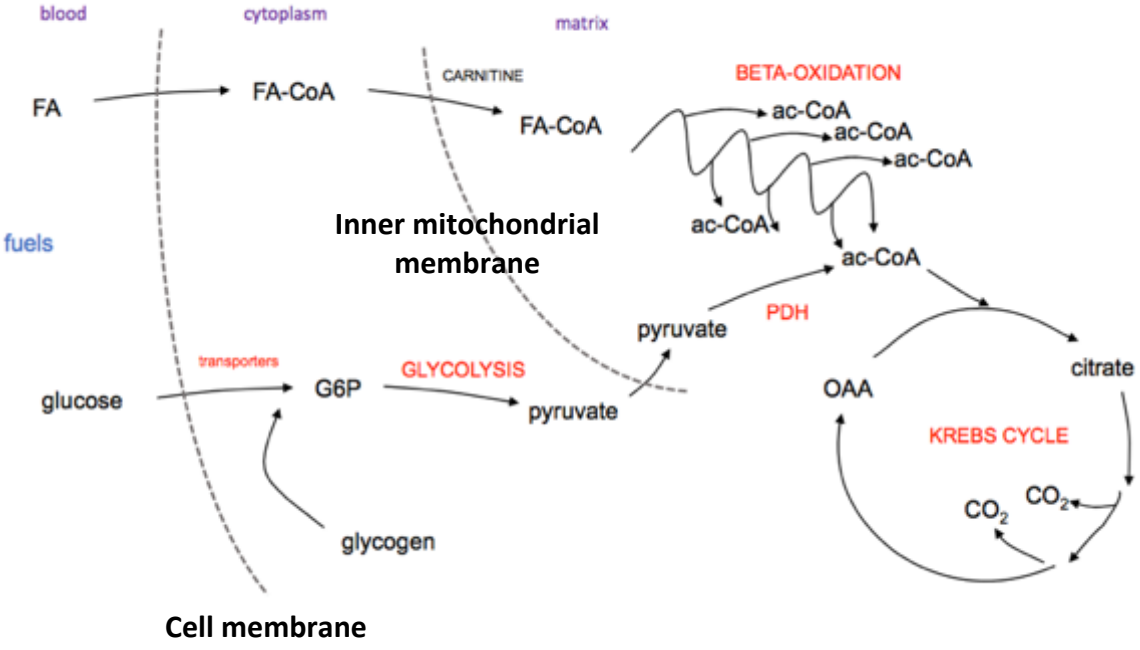
- ATP turnover is very high in relation to stores even at rest.
  - *Store:* 1g/kg body weight – levels held in very narrow range (btwn 5mM and 3mM)
  - *Turnover:* 1kg/kg body weight

This is all causes by the process of coupling – i.e. we are generating ATP because 1 few microseconds previously, we have used ATP.

Major Pathways of Fuel Oxidation

Major fuels used
1. Fatty acids
2. Glucose

- Fuels → CO_2



Note: the oxygens from the carbon dioxide actually come from the fuels and not gaseous oxygen.

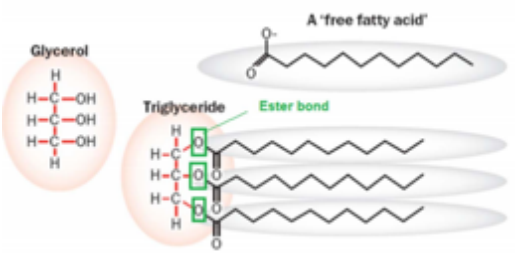
Fuels: *Fatty Acids*

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2\text{------}CH_2CH_2COOH$$

- Long hydrocarbon chain with a carboxylic acid group
- Nearly all the carbon atoms are fully reduced (all have hydrogens on them).

- Stored as triglyceride – 3 fatty acid molecules esterified to a molecule of glycerol.
  - Totally hydrophobic
  - Very energy dense (37 kJ/g)
  - Hugh stores (many kg)

- However, can't be used by the brain



The process in which fat is oxidized is called…

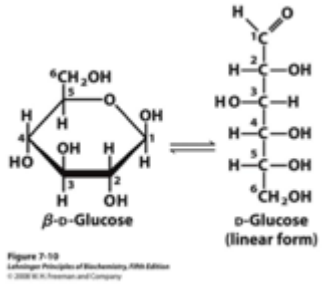
Beta-oxidation

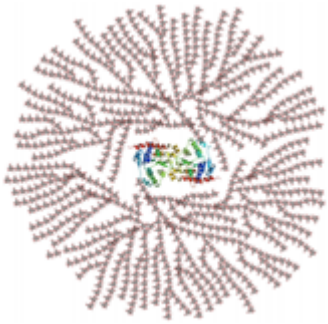
- Every time 2 H+ and e- molecules are ripped off the fatty acid, 2 carbon atoms are released.

Overview of process: Fatty acid is trapped in cytoplasm as Fatty Acyl-CoA → transported into mitochondria (carrier being carnitine) → H/e- ripped out by FAD and NAD → fatty acids part loses an acetate chunk → cycle repeats.

Fuels: *Glucose*

- *Reasonably* reduced
- Stored as glycogen
  - Hydrophilic, lots of water associated
  - Inefficient; 16 kJ/g (but only 6 kJ/g wet)
  - Low stores (300 g)
- Can be used by all tissues
- Brain obligatory requirement
  - Stored in association with water
  - Broken down very quickly because of the branched structure



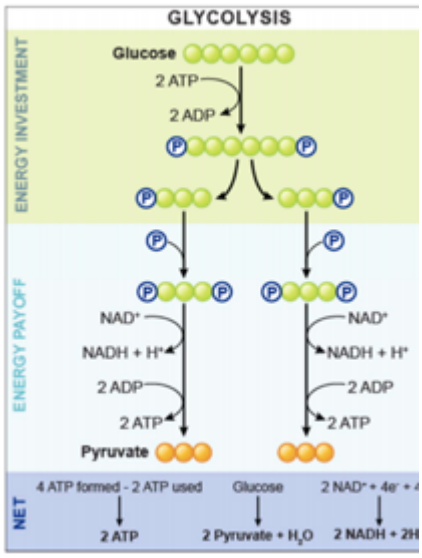


Glucose oxidation

Glycolysis

- Completely cytosolic i.e. does not require mitochondria
- Very fast, but very efficient
- No requirement for oxygen

- Pyruvate transported into mitochondria for oxidation.



Gentle exercise

With gentle exercise, we generate ATP are a relatively slow rate, manageable with oxidative phosphorylation, increase activity of beta or glyosidic oxidation.

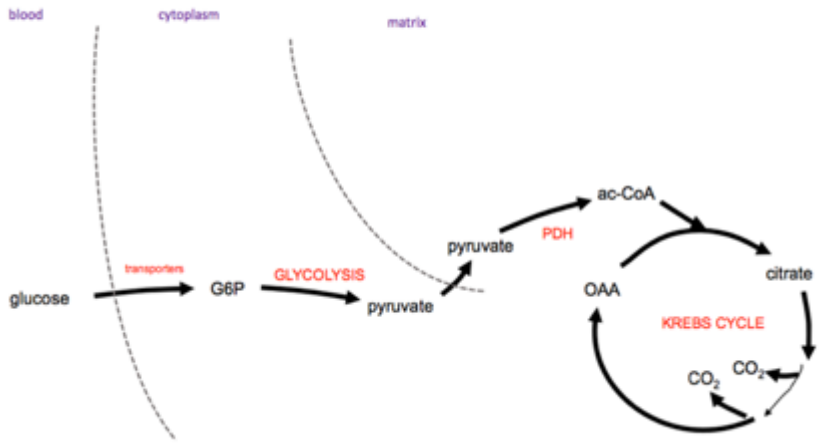
But our body uses the most readily available fuel in the blood stream. Glucose transporters will move to the cell surface.

However, this lowers blood glucose – and we need to keep it at 5mM for our brains.

This triggers glucose homeostasis activity → tiny decrease in blood glucose gives a big hormonal response

- Insulin goes down (would be high if glucose was high in our bloodstream)
- Glucagon goes up

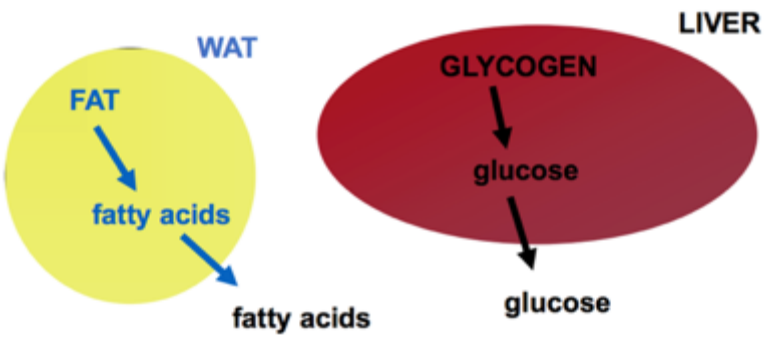
Pathway activated:



Effects of hormonal changes

1. Stimulation of glycogen breakdown in liver (which is the main store)
    a. Hydrolyses glycogen, to increase glucose in bloodstream (for the brain)

2. Stimulation of fat breakdown in white adipose tissue – as alternative fuel.

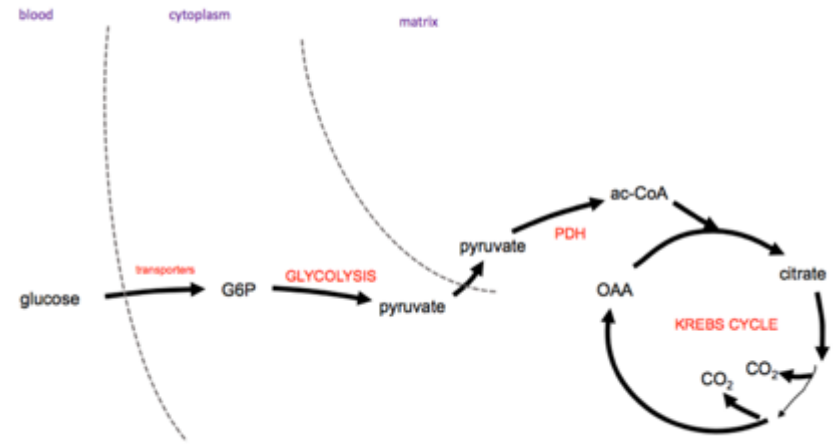


Glucose Recycling

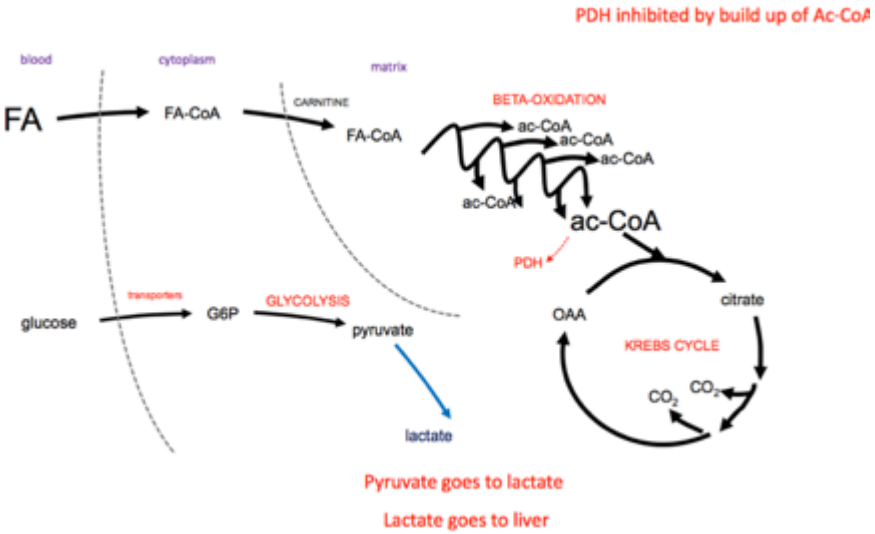
- We want the cells in our body to stop using glucose, and start using fatty acids as fuel sources.
- We don't want to burn our glucose; stop the process are a state where it can still be recycled.

Glucose stores (glycogen) are limited and we cannot convert fatty acids into glucose. Instead, we substitute glucose for fatty acids as fuel. This then prevents glucose from being wastefully oxidized.

Without fatty acid oxidation:



With fatty acid oxidation:

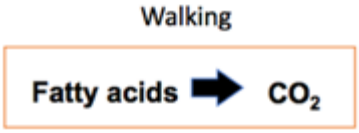


Note: Whenever we oxidize fatty acid, we tend to reduce the oxidation of glucose, which is good because it is in short supply and needed by the brain.

Glucose will still be absorbed into the cells because of the transporters because will only get to the pyruvate, and instead converted to lactate/lactic acid, diffusing out of the cell and return to the liver for recycling.

What is actually happening during…

Gentle exercise



1. Initially glucose is used.

2. After several minutes, fatty acids take over,
   - Released from white adipose tissue

3. Glucose still gets into the muscles
   - Only taken as far as lactate

4. Lactate goes to liver for resynthesis of glucose
   i.e. gluconeogenesis

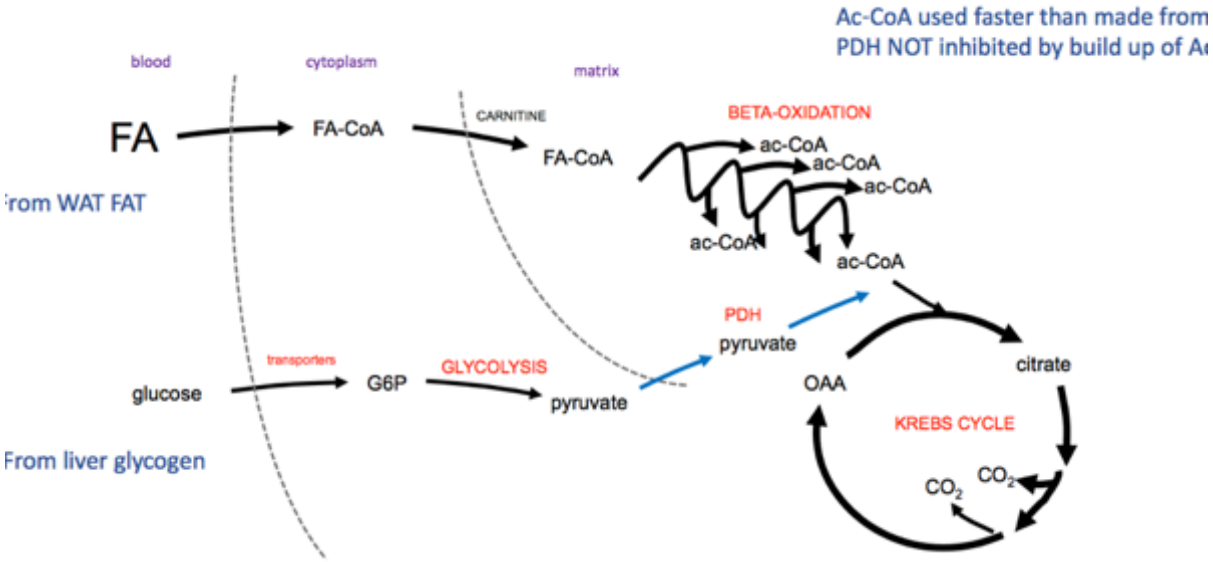
   Note: lactate doesn't build up because the rate at which is produced is similar to the rate at which the liver efficiently converts it back to glucose.

Moderate exercise

1. As pace increases –
   The rate of fatty acid utilization increases, because '**' but…
   - The enzymes that catalyze fatty acid oxidation soon reach their maximum capacity – we can't deliver ac-CoA quick enough to the KREBS cycle; i.e. Krebs cycle is faster than beta-oxidation.

2. Fatty acid oxidation alone cannot maintain ATP production
   Then, the inhibition on glucose oxidation is removed

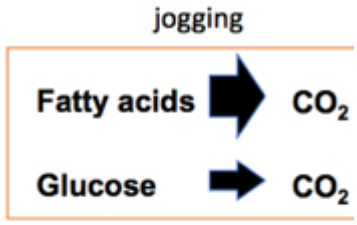
3. Glucose oxidation occurs
   Less glucose recycling, liver glycogen stores depleted faster.



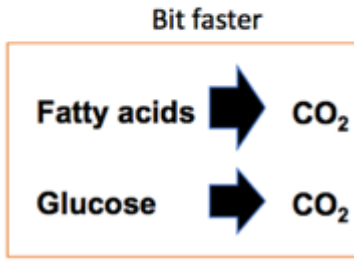
Note:

In moderate exercise there is a mixture of fatty acid oxidation and glucose oxidation; with the glucose coming from the liver

- When this occurs is largely dependent on the intensity of the exercise or fitness i.e. how efficient beta oxidation is for the individual.



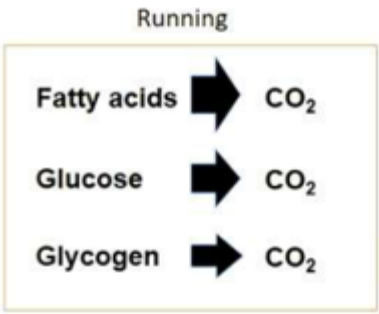
Any further increase in the pace is met by increase in glucose oxidation – **fatty acid oxidation is already at capacity –** *not that we are stopped using fat.*

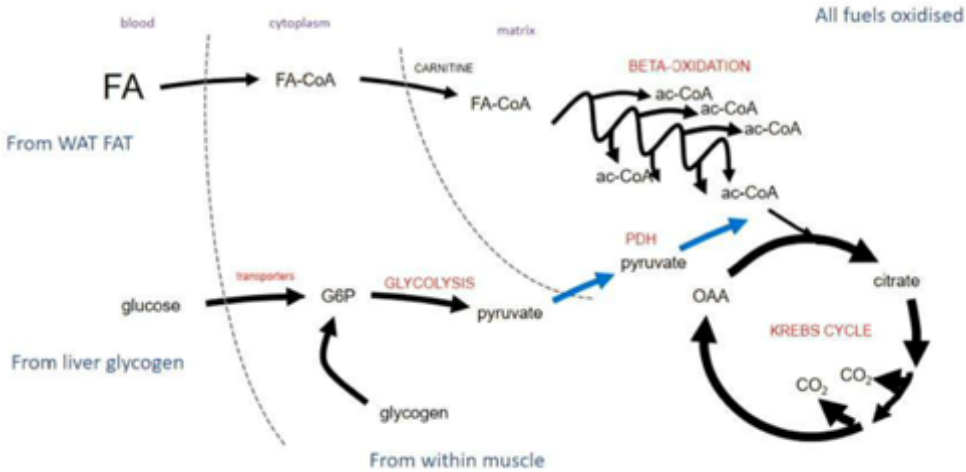


Strenuous Exercise

1. There is now a limit of the speed of oxidation of blood glucose – the rate of supply and transport from the blood can't keep up.
   - Fatty acids are still going at capacity

2. Muscle glycogen is broken down.
   - Endogenously stored i.e. stored within the muscle so does not need to be transported.





Even more strenuous exercise

1. Now ATP production cannot be met by oxidative phosphrylation alone.
   - Mitochrondrial processes is too slow
   - ETC has a limit – dependant on fitness, i.e. the amount of carriers to strip H/e- from the fuels and transport to the ETC.

2. Needs to top up with extra boost from glycolysis
    - Glycolysis is very fast because it is a totally enzymic process.

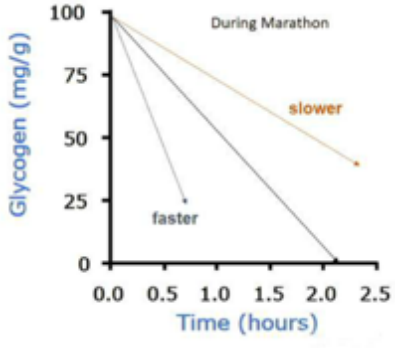
    - It is very inefficient; because we don't have carriers bringing in more glycogen – Therfore, pyruvate will be converted to lactate at a rapid rate – to regenerate the carriers.

Why glycogen is important

When glycogen has run out, only fatty acid oxidation can be used for ATP generation. But power output is lower whne only using fatty acids – we call this "hitting a wall" in marathon running.

- Cannot sprint if there is no glycogen.

    When athlete run out of glycogen, it is most likely they have run out of both muscle and liver glyogen, so the brain has no more fuel.

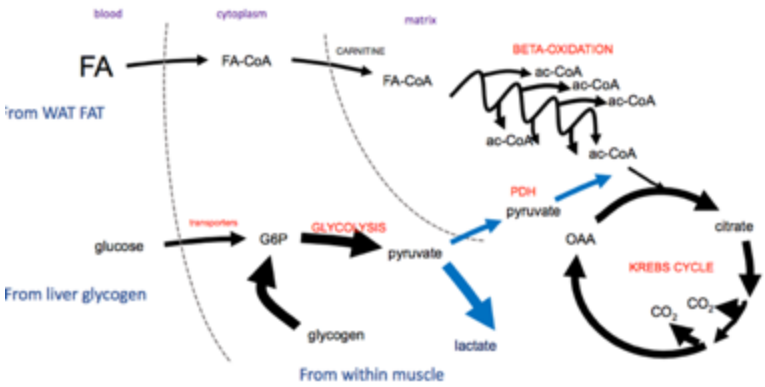


Sprinting

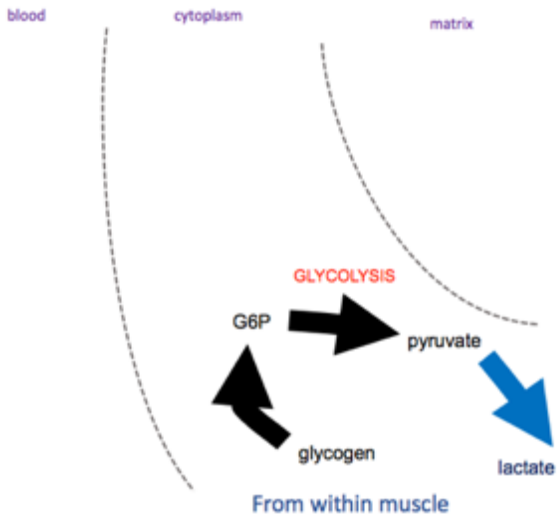
- Intense exercise that recruits Type IIb muscles
    - Fibers where have poor blood supply, packed full of contractile filaments, few mitochondria and very rapid consumption of ATP.

In this case we have a fuel selection problem – cannot use *fatty acids* because of the poor oxygen supply and low mitochondria and cannot use *blood glucose* because of the delay in transporter recruitment, poor fuel supply, low blood supply

- Won't use anything from the blood.



Note: **everything comes from the blood stream except… glycogen!**



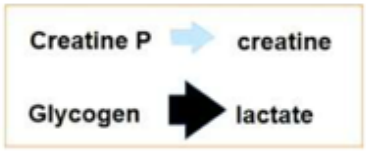
Note: consumes ATP at the absolute maximum rate. Happens very fast, producing lots of lactate. But because the blood supply is bad, the lactate will be difficult to get rid of and thus build up in the muscle. As it is acidic, i.e. lactic acid, it will interfere with the contractions of the muscle.

<u>Buying time</u>

- It is difficult to get this pathway started immediately, therefore we need to buy time.

It takes several seconds to get glycogenosis going.

Creatine Phosphate (CP) is an instant store of ATP. But there is less than 5 seconds of supply (15 mM).



As soon as an ATP molecule is consumed, it will immediately be transformed back to ATP via CP; no need for glycolysis.

creatine phosphate + ADP → ATP + creatine