Integration and regulation of metabolic pathways

BIO-213, Exercises 12 Solutions

Question 1

ATP and phosphocreatine are energy sources for our muscles. During muscle contraction phosphocreatine [] drops while that of ATP [] remains roughly constant.

1) How do you explain this?
2) When treated with a creatine kinase inhibitor a contracting muscle shows a rapid drop in [ATP] with little effect on [phosphocreatine]. How do you explain this?

Question 1

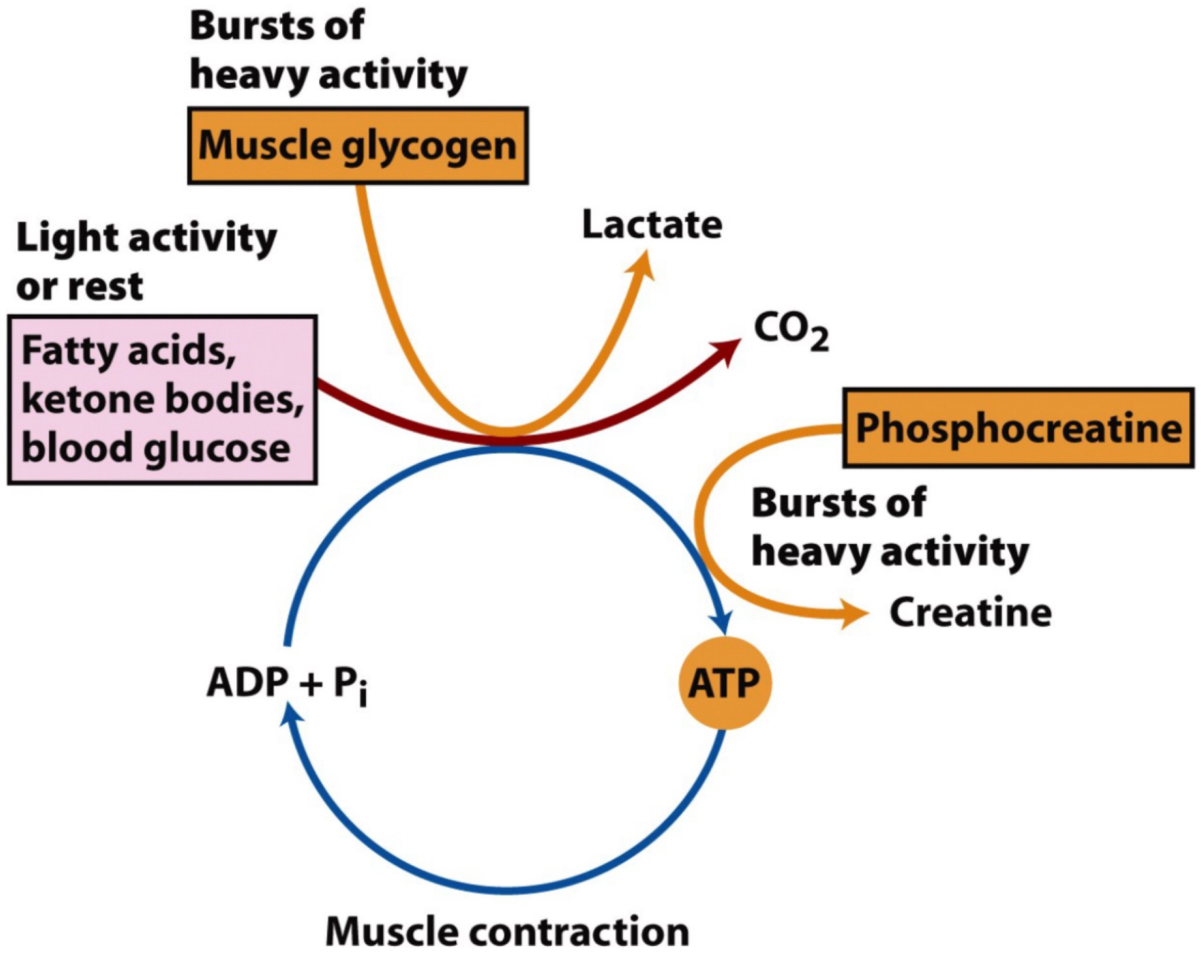
ATP and phosphocreatine are energy sources for our muscles. During muscle contraction phosphocreatine [] drops while that of ATP [] remains roughly constant.

1) How do you explain this?

Phosphocreatine is used to **regenerate ATP** from ADP by the **creatine kinase reaction**.

During muscle contraction, the reaction proceeds predominantly in the direction of ATP synthesis.

During recovery the same enzyme synthesises phosphocreatine from creatine and ATP.



See: Lecture 11, slide 10

Question 1

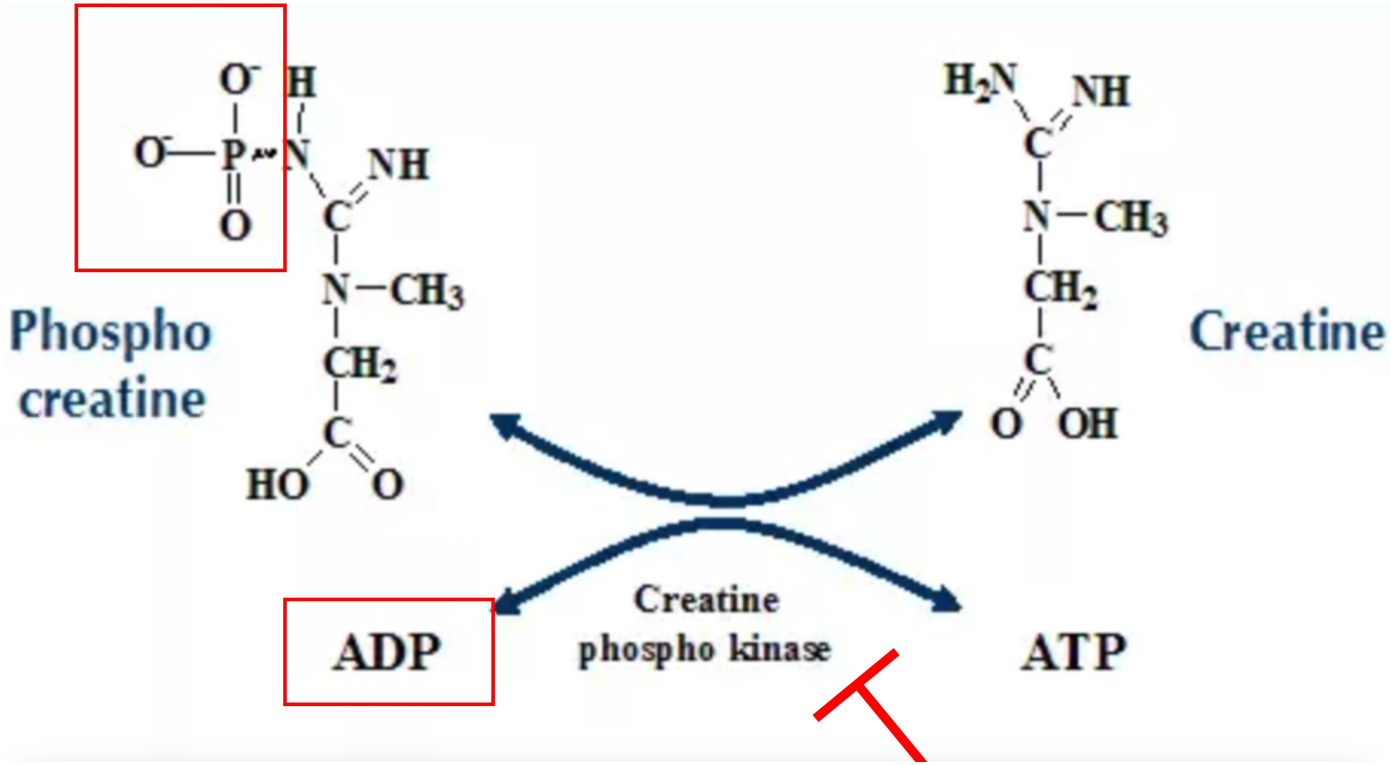
ATP and phosphocreatine are energy sources for our muscles. During muscle contraction phosphocreatine [] drops while that of ATP [] remains roughly constant.

1) How do you explain this?
2) When treated with a creatine kinase inhibitor a contracting muscle shows a rapid drop in [ATP] with little effect on [phosphocreatine]. How do you explain this?

ATP is used as an energy source for contracting muscle. Since the reaction of creatine kinase is inhibited the phosphocreatine cannot be used to regenerate the ATP pool:

→ ATP levels drop

→ Phosphocreatine levels remain stable



Question 2

Patients affected by acute pancreatitis are treated with IV injection of a solution containing glucose and NaCl, while they are asked to avoid proteins in their diet.

1) Can you explain the basis of this treatment?
2) While treated these patients develop hyperglycaemia. Can you explain why?

Question 2

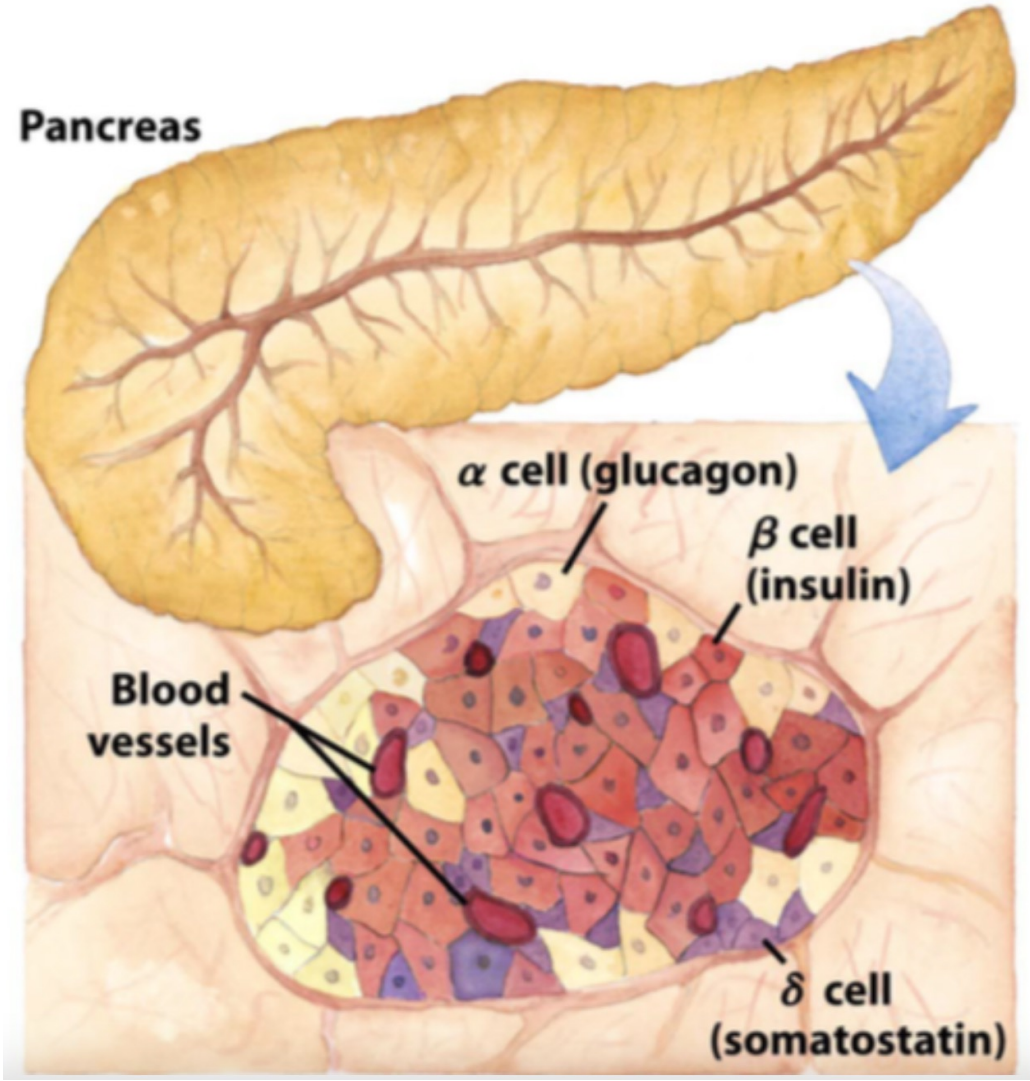
Patients affected by acute pancreatitis are treated with IV injection of a solution containing glucose and NaCl, while they are asked to avoid proteins in their diet.

1) Can you explain the basis of this treatment?

Acute pancreatitis: inflammation of pancreas due to destruction by its own digestive enzymes. Obstruction by gallstones of the normal pathway by which pancreatic secretions enter the intestine. Proteolytic enzymes are converted to their catalytically active form prematurely inside the pancreatic cells and attack the pancreatic tissue itself.
→ Damage to cells producing glucagon and insulin

IV injection with glucose and NaCl
IV fluids help to restore and maintain blood volume and pressure
→ NaCl helps to restore electrolyte imbalances, maintain electrolyte homeostasis, and drives water uptake.
→ Glucose provides a source of calories and help maintain blood glucose levels

Avoiding proteins in diet:
→ High protein can cause gallstones, which are a major cause of AP
→ Minimizes pancreatic stimulation and prevent further injury



See: Lecture 11, slide 14

Question 2

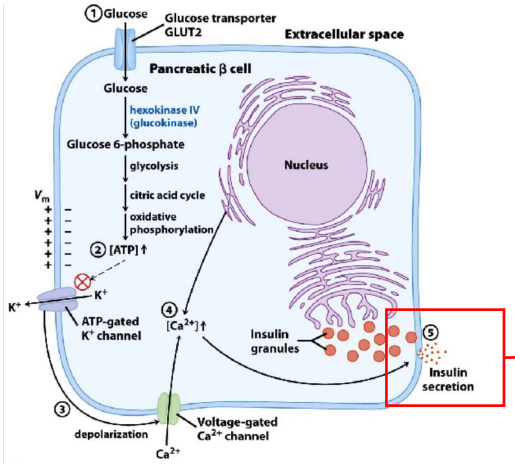
Patients affected by acute pancreatitis are treated with IV injection of a solution containing glucose and NaCl, while they are asked to avoid proteins in their diet.

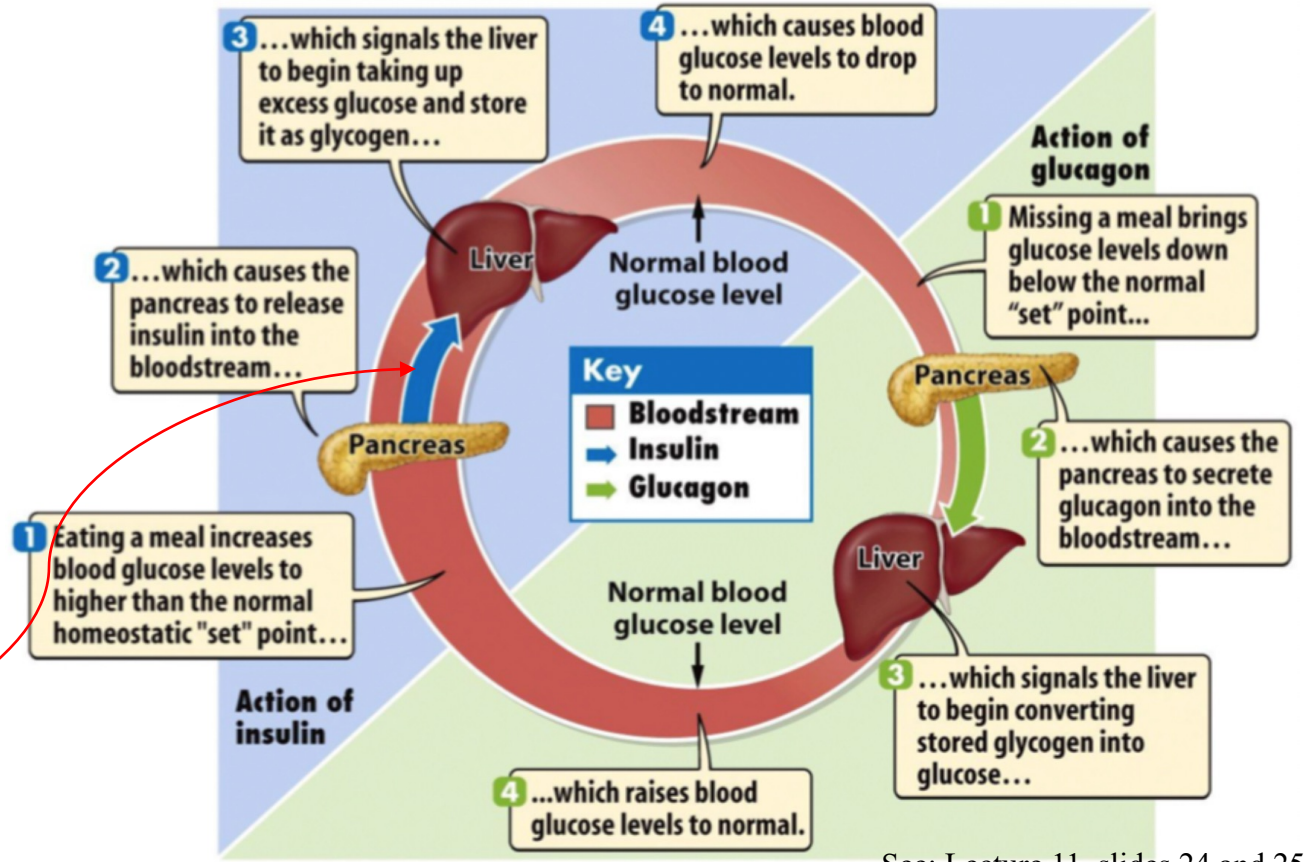
1) Can you explain the basis of this treatment?
2) While treated these patients develop hyperglycaemia. Can you explain why?

Hyperglycaemia: Increased glucose in blood.

Acute pancreatisis causes damage to pancreatic beta cells producing insulin.

→ Result: no insulin secretion, liver does not take up excess glucose, and glucose remains in blood.





See: Lecture 11, slides 24 and 25

Question 3

While resting a human being consumes 0.05 L of oxygen in 10 sec. During a 100 m sprint run this consumption raises to 1L in 10 sec. After the run in some minutes the sprinter consumes 4L of oxygen more than he/she would have consumed if in resting conditions.

1) Why during the sprint the consumption of oxygen raises so dramatically?
2) Why the oxygen demand remains high also after the run is over?

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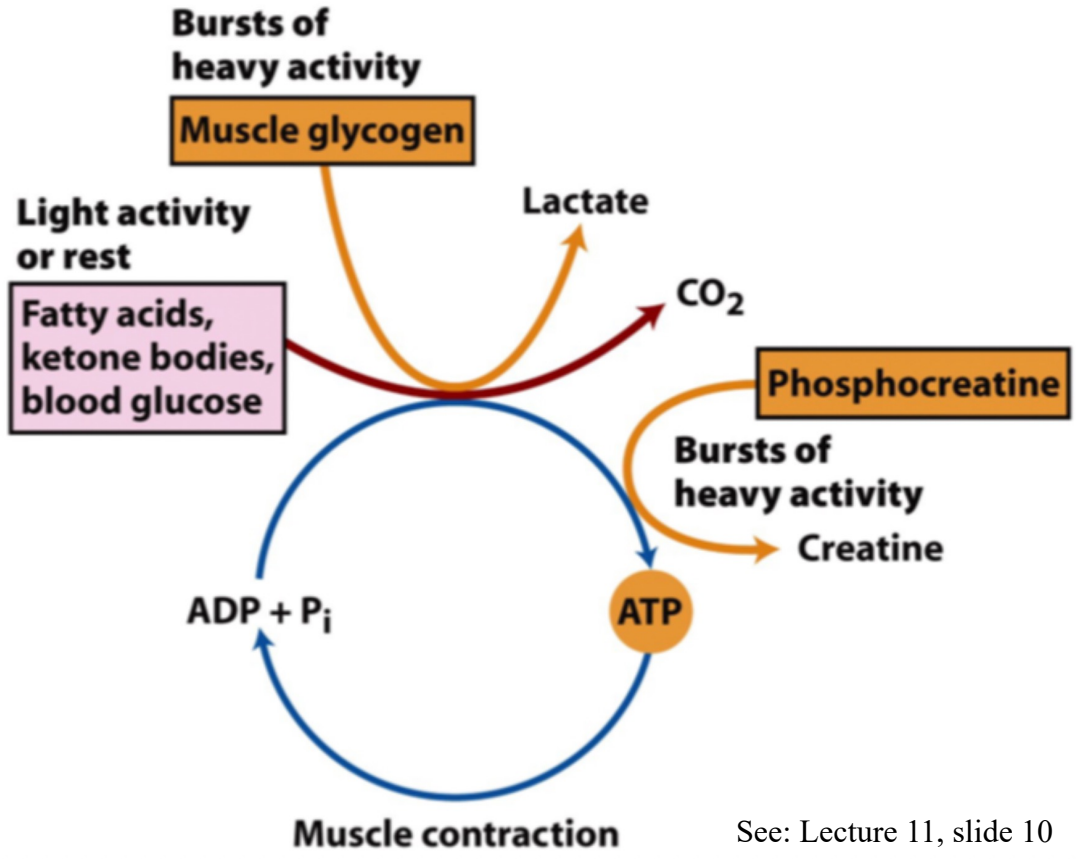
1) Why during the sprint the consumption of oxygen raises so dramatically?

Muscle contraction uses aerobic respiration. However, during intense activity, like sprinting, muscles turn to **anaerobic respiration** to meet their ATP needs. Resulting in **build up of lactate**.

To get rid of lactic acid we need to transport it from muscles through blood to liver where it will **react with oxygen**.



See: Lecture 11, slide 10

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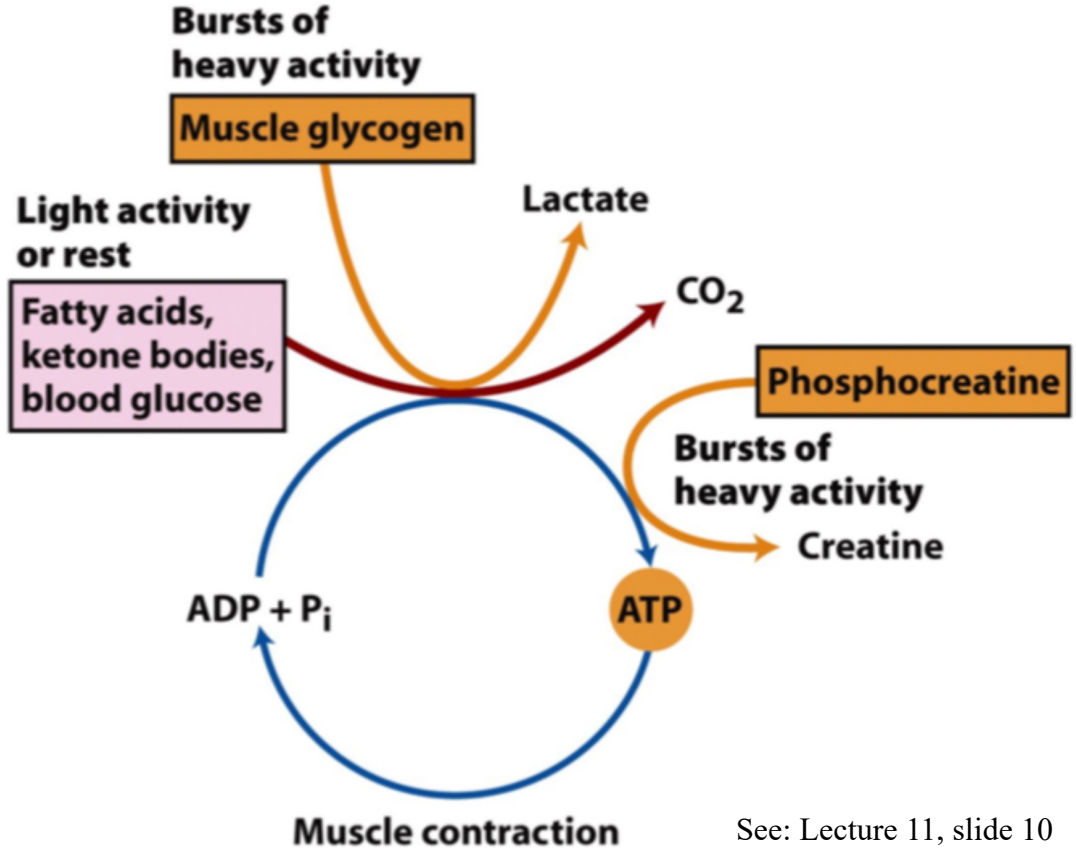
1) Why during the sprint the consumption of oxygen raises so dramatically?
2) Why the oxygen demand remains high also after the run is over?

To get rid of lactic acid we need to transport it from muscles through blood to liver where it will **react with oxygen**.

Post exercise recovery = "**oxygen debt**"
→ Recover from lactic fermentation
→ Hormone balancing
→ Replenish glycogen
→ Replenish ATP stores and phosphocreatine
→ Cellular repair



Short youtube video explaining oxygen debt:
https://www.youtube.com/watch?v=PthdswsrM3Y

See: Lecture 11, slide 10

Question 4

The half-life of the hormones in the blood is relatively short. Insulin for instance survives in the blood stream for little more than 30 min.

1) What is the importance of having a short half-life for hormones
2) How are the hormone levels are kept constant in the light of their short half-lives
3) How does the organism manages to rapidly increase the circulating [] of an hormone on demand?

Question 4

The half-life of the hormones in the blood is relatively short. Insulin for instance survives in the blood stream for little more than 30 min.

1) What is the importance of having a short half-life for hormones

Rapid Response and adjustment

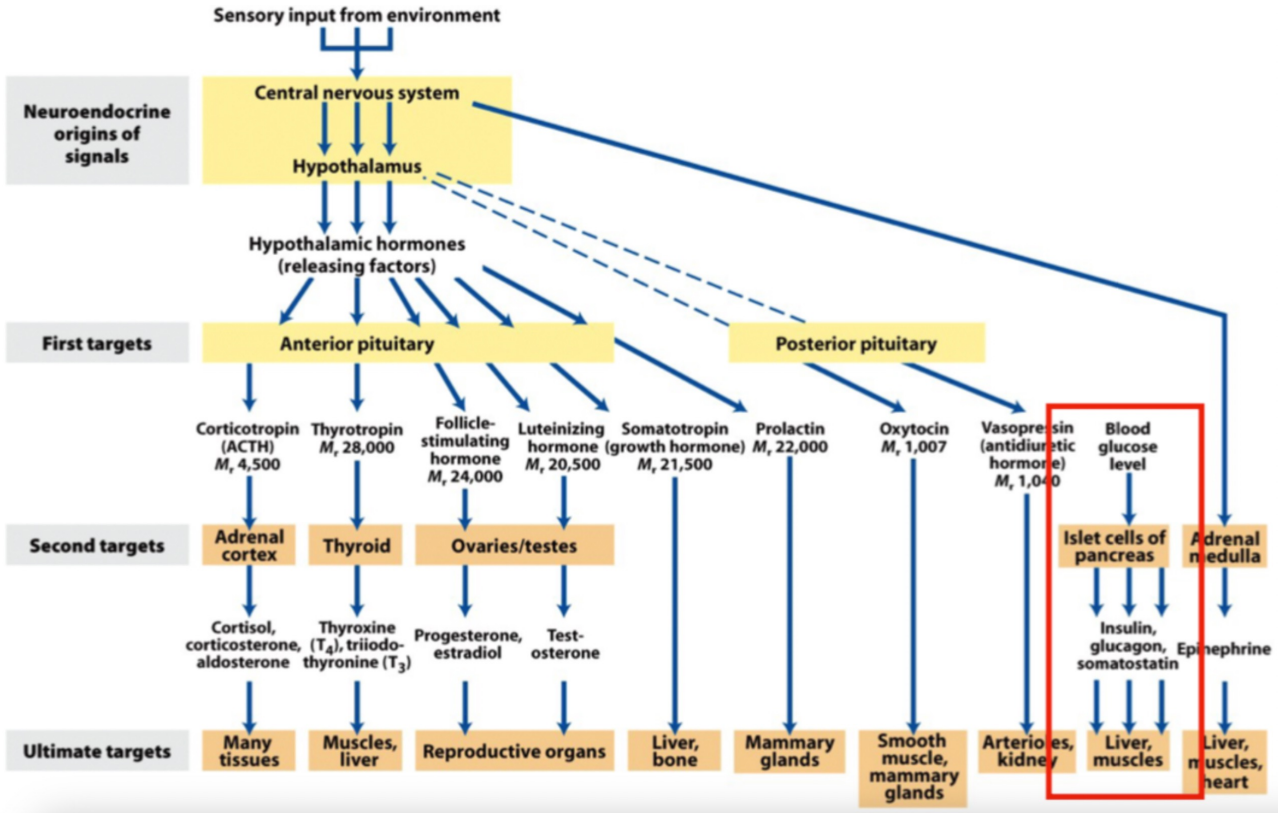
Short half-life allows for rapid changes in hormone concentrations → fast response to varying physiological demands

e.g. insulin needs to act quickly after the meal to lower the glucose levels in the blood. Its short half-life ensures it is cleared from the bloodstream rapidly once the glucose levels are normalised.

Prevention of prolonged effects

Prolonged presence would overstimulate the target tissues → disruption of homeostasis

e.g. insulin: prolonged stimulation leads to hypoglycaemia



See: Lecture 11, slide 23

Question 4

The half-life of the hormones in the blood is relatively short. Insulin for instance survives in the blood stream for little more than 30 min.

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2) How are the hormone levels are kept constant in the light of their short half-lives

Regulatory systems of feedback loops and rapid synthesis

Feedback Loops

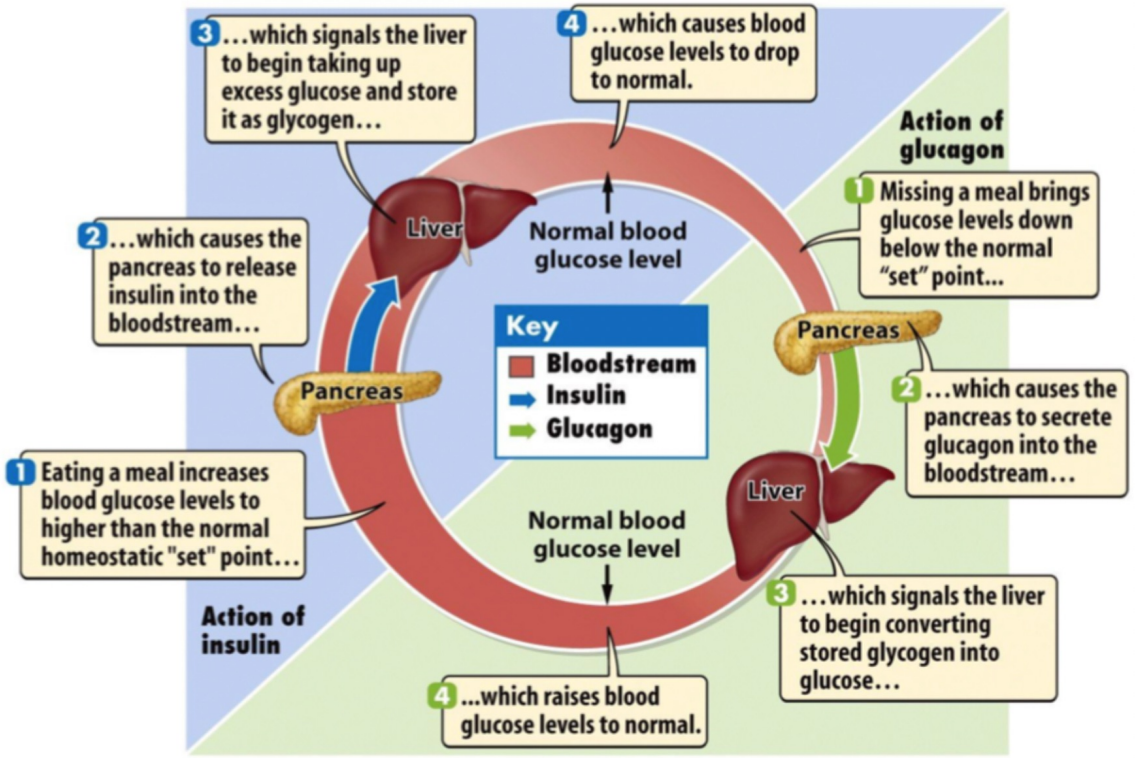
→ Negative: when hormone's effects reaches certain level, it inhibits further secretion of that hormone

→ Positive: increased levels lead to further increase (less common)

Rapid synthesis on demand by hormone producing cells in response to specific stimuli.

Hormone degradation enzymes act quickly so that levels do not remain elevated for too long.

Equilibrium between hormone synthesis and degradation = stable hormone concentrations



Example of a feedback loop

See: Lecture 11, slide 25

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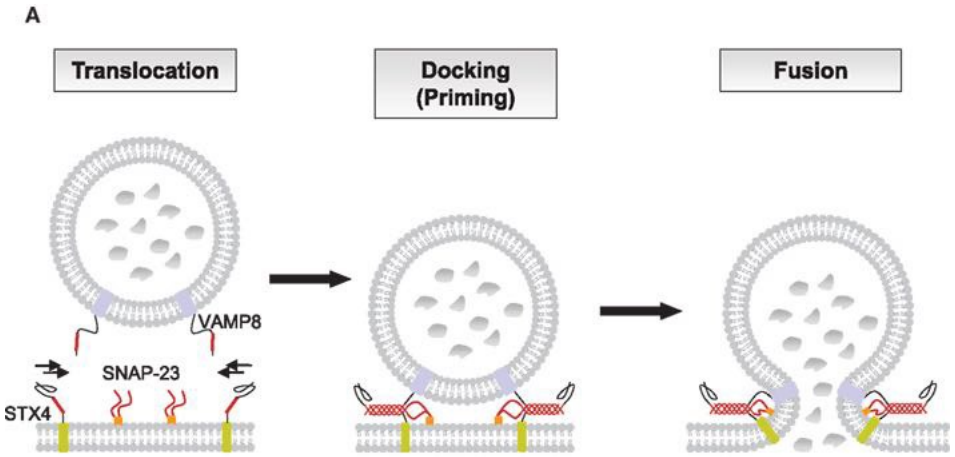
3) How does the organism manages to rapidly increase the circulating [] of an hormone on demand?

Biosynthetic cells can produce and store biologically inactive forms of hormones (pre-hormones)

Peptide hormones (insulin): precursor protein packaged into secretory vesicles and proteolytically cleaved to form the active peptide



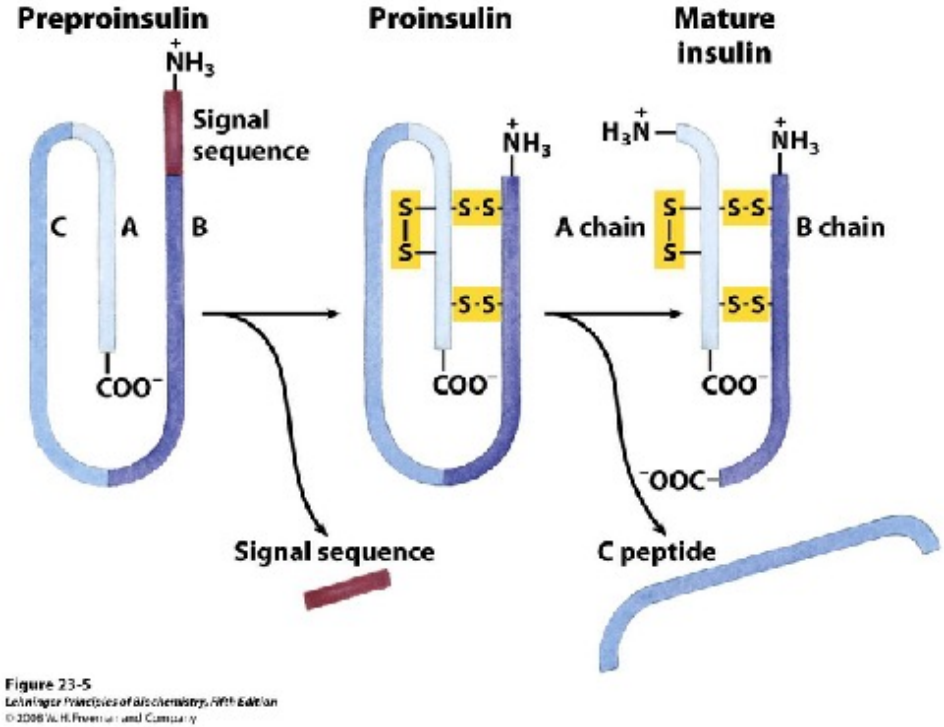


Figure 23-5

See: Lecture 11, slides 28 and 29

Question 5

Some pancreatic cancers lead to excessive insulin production/ secretion by beta-cells. Patients affected by these cancers experience tremors, weakness, sweating and hunger. If prolonged this condition can lead to brain damage.

1) what is the effect of excessive insulin secretion on the metabolism of (a) sugars; (b) lipids; (c) amino acids in the liver?
2) what are the causes of the observed symptoms? Why this condition can lead to brain damage?

Question 5

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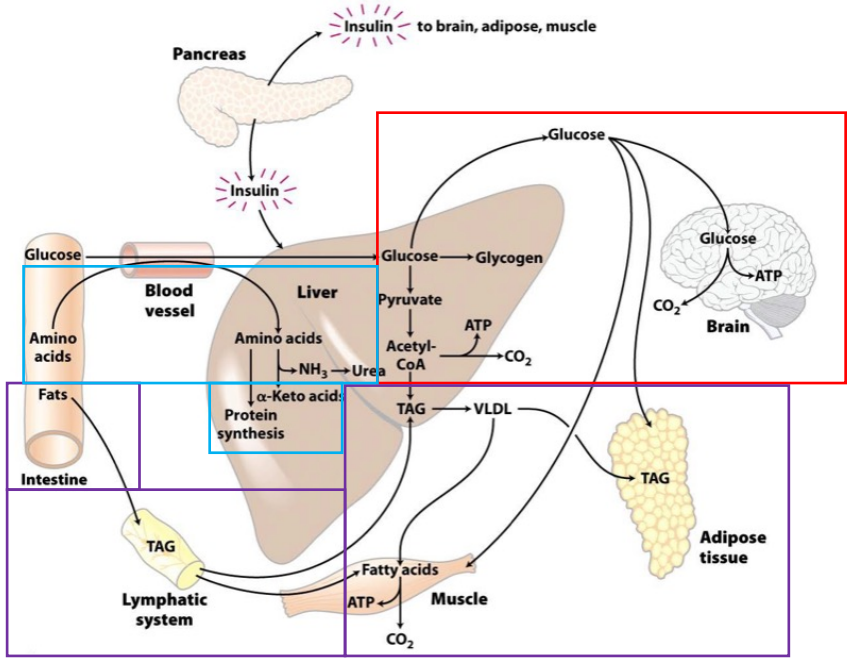
TABLE 23–3 Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	Target enzyme
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by ↑ PFK-2) ↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase



(a) Sugars → increased glucose uptake and glycolysis

(b) Lipids → increased fatty acid synthesis

(c) Amino Acids → increased amino acid uptake and protein synthesis

See: Lecture 11, slides 31 and 32

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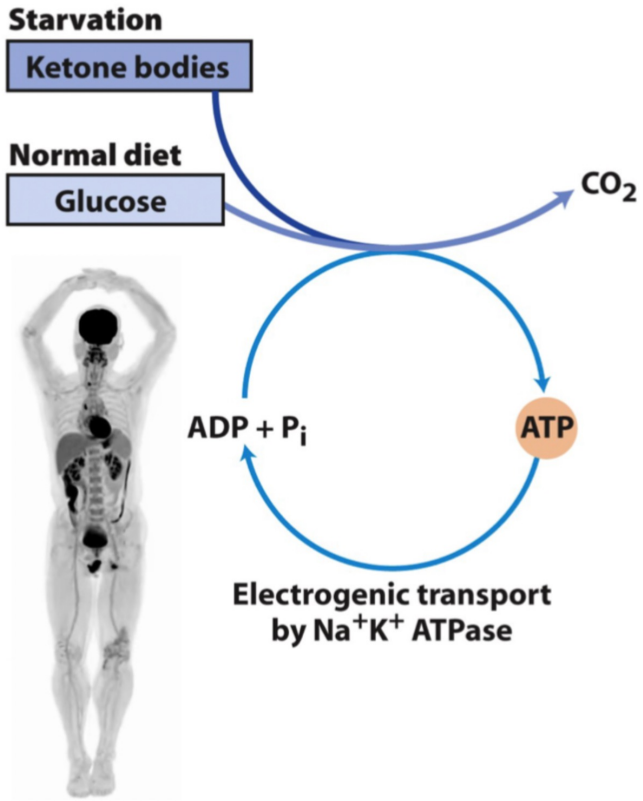
1) what is the effect of excessive insulin secretion on the metabolism of (a) sugars; (b) lipids; (c) amino acids in the liver?
2) what are the causes of the observed symptoms? Why this condition can lead to brain damage?

Causes:

→ Cells absorb too much glucose
→ Liver releases less glucose
→ Blood glucose levels drop

Why brain damage?

→ The brain has limited glycogen storage, therefore relies on glucose circulating in the blood.
→ 90 % of the ATP in the brain comes from glycolysis → TCA → oxidative phosphorylation.
→ Neurons cannot directly use fatty acids or lipids from the blood as fuel, but they can oxidatize β-hydroxybutyrate (in ketone bodies) when in starvation mode.



See: Lecture 11, slide 12

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1) what is the effect of excessive insulin secretion on the metabolism of (a) sugars; (b) lipids; (c) amino acids in the liver?
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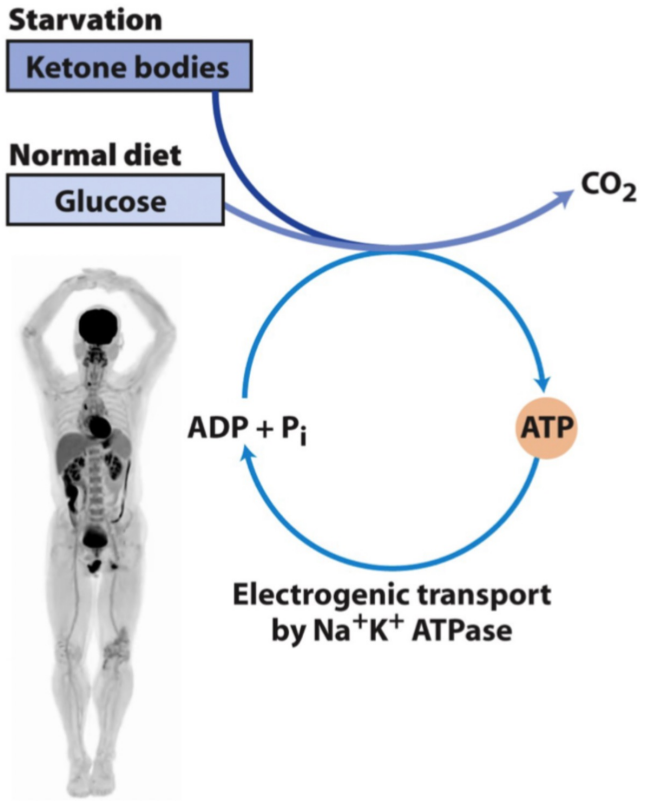
Why does the brain need so much ATP?

→ Neurons maintain an electrical potential across their plasma membranes via Na^+ K^+ ATPases, which simultaneously pump 2 K^+ ions into and 3 Na^+ ions out of the neuron. Neurons need this electrical potential to produce action potentials, the basis of nervous system signaling.

→ For perspective: brain activity accounts for 20% of oxygen consumption in a human being at rest (OxPhos).

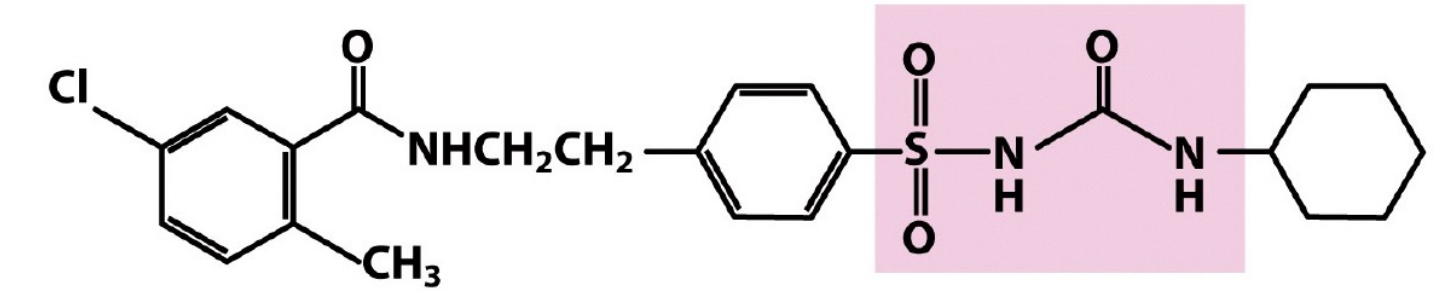


See: Lecture 11, slide 12

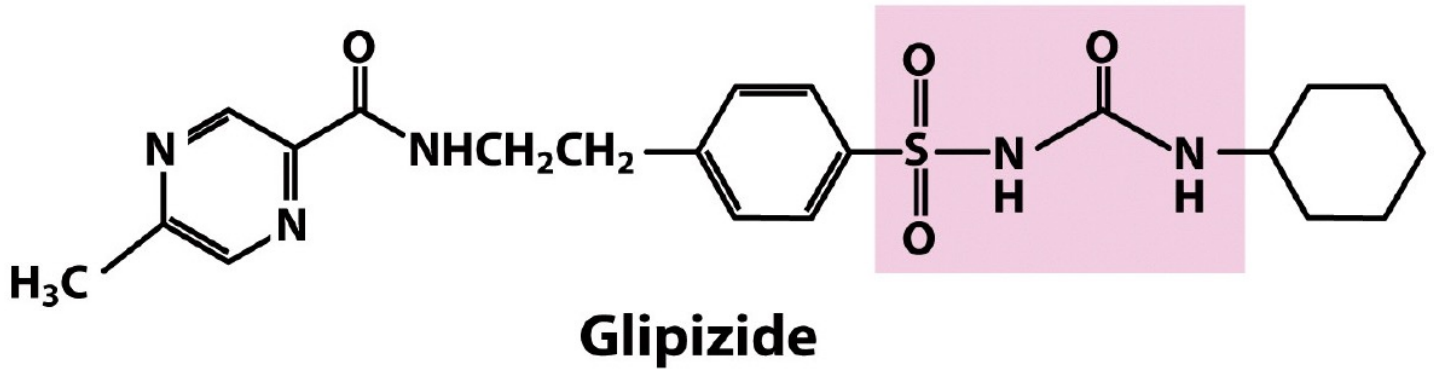
Question 6

Glyburide and Glipizide are molecules that bind to SUR1 leading to the inhibition of the function of KATP channels in pancreatic beta- cells.

Which condition can be treated with these drugs? Explain your answer.



Glyburide



Glipizide

Question 6

Glyburide and Glipizide are molecules that bind to SUR1 leading to the inhibition of the function of KATP channels in pancreatic beta- cells.

Which condition can be treated with these drugs? Explain your answer.

Inhibition of KATP channels leads to:

1. Accumulation of K^+ inside the cell.
2. Depolarization of voltage-gated Ca^{2+} channels.
3. Increase of Ca^{2+} concentration inside of the cell.
4. Increase of Ca^{2+}-mediated insulin secretion.
5. Increase in insulin production (the more insulin secreted, the more beta cells will produce).

Glyburide and Glipizide thus promote insulin secretion and production.

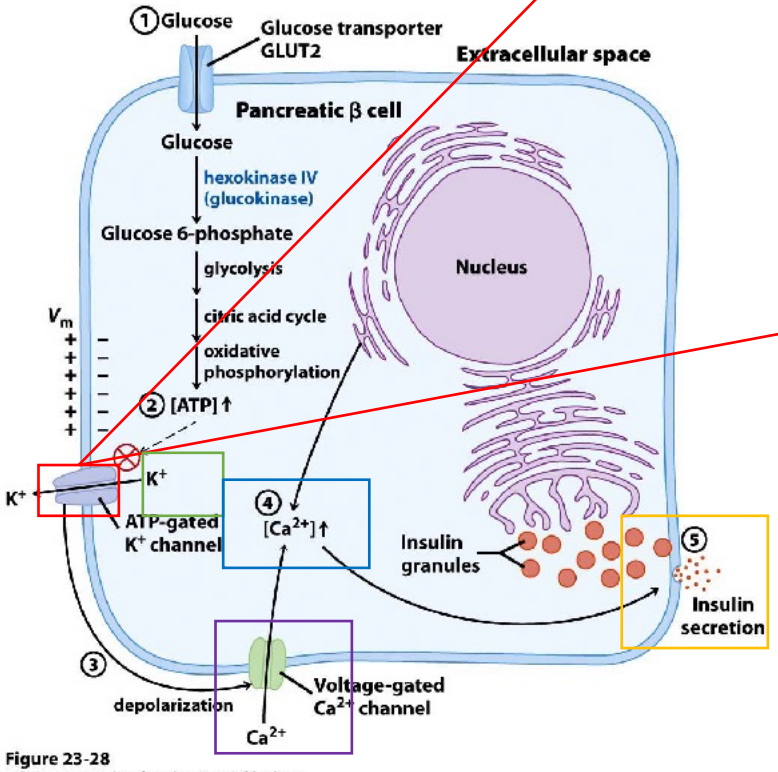


Figure 23-28
Lehninger Principles of Biochemistry, Fifth Edition
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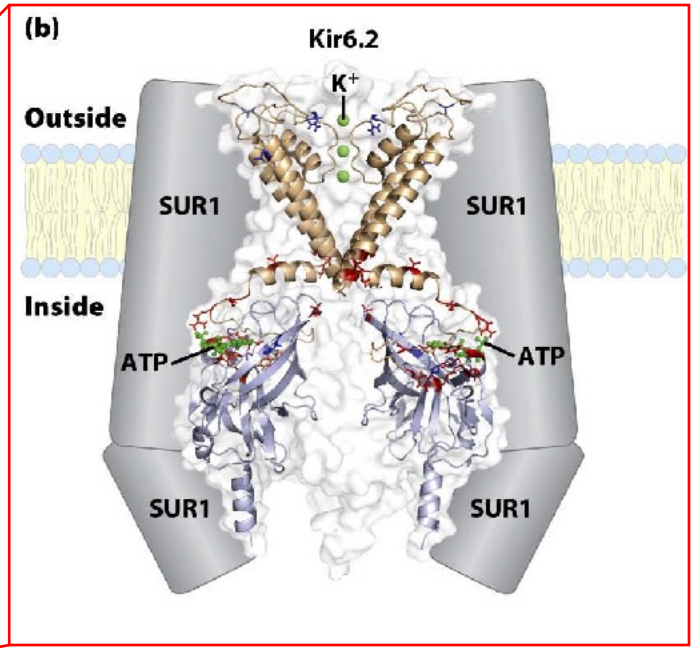
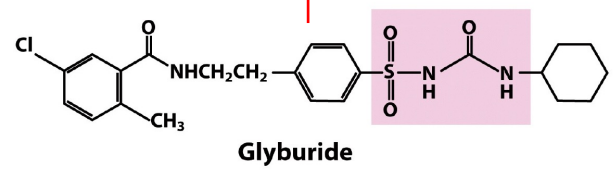
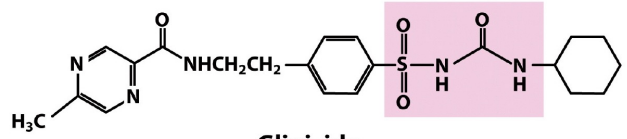




Glyburide



Glipizide

See: Lecture 11, slides 26 and 27

Question 6

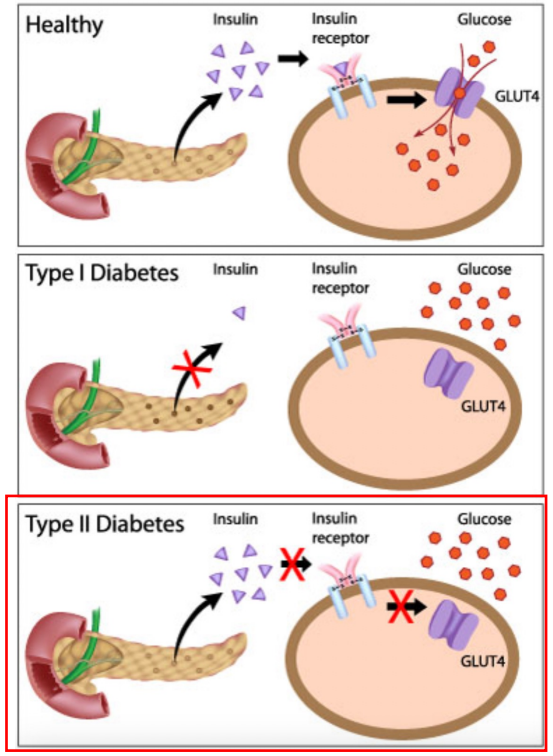
Glyburide and Glipizide are molecules that bind to SUR1 leading to the inhibition of the function of KATP channels in pancreatic beta- cells.

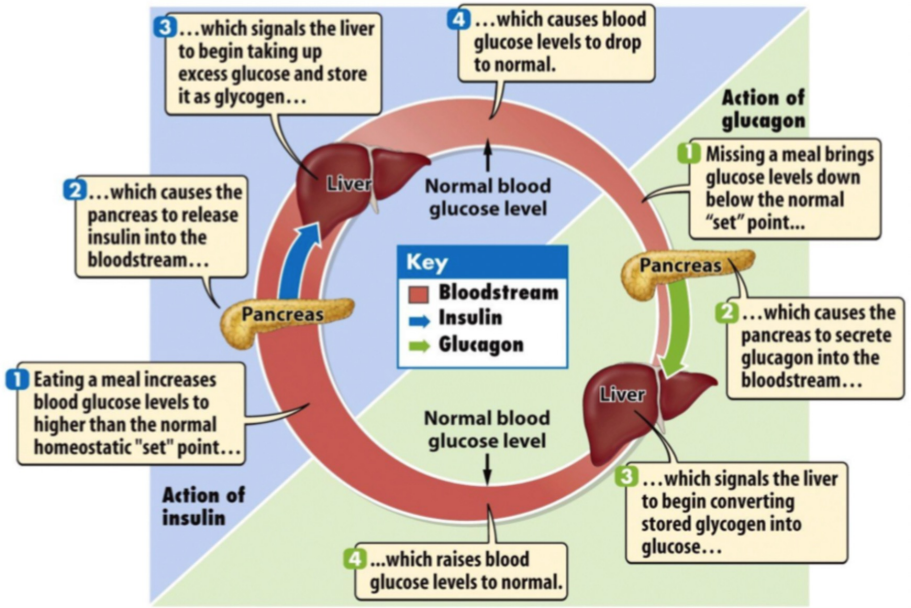
Which condition can be treated with these drugs? Explain your answer.

Glyburide and Glipizide promote insulin secretion and production.

These drugs can be used to treat Type II diabetes by increasing insulin concentration in the blood and making insulin receptors more likely to respond appropriately to insulin signaling.

Physiological effects:
→ Promotion of cellular glucose uptake.
→ Decrease in blood glucose levels.
→ Combats hyperglycaemia.





See: Lecture 11, slides 24 and 37