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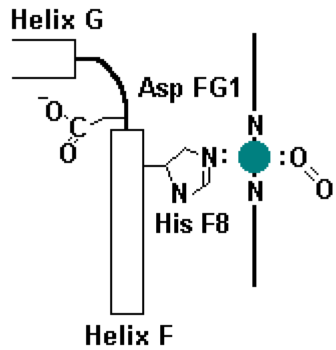
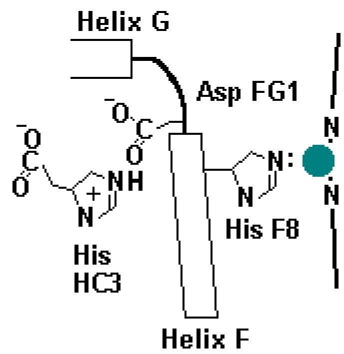
21. The figures represent the environment around heme in β-globin.

Identify which represents T-state and which is R-state (1 mark)

What component of the opposite α-globin interacts with His HC3?



State: __**R**___



State: _ **T**____

___ **Lys** (1) **C5**_(1)_____________ (2 marks)

Briefly explain how the presence of His HC3 is responsible for low O_2 affinity. (3 marks)

In T-state, His HC3 can form an ion pair with Asp FG1 on the same b-globin

Tension from this ion pair pulls Helix F away from heme

His F8 pulls Fe^{2+} out of the heme plane, making it less accessible to O_2 in the ligand 6 position

How will an increase in pH help shift to R-state? (3 marks)

Higher pH causes His HC3 side chain to deprotonate and lose its charge

This breaks the ion pair with Asp FG1

Helix F and the Fe^{2+} relax to their natural state

When O_2 binds in one or two sites of hemoglobin, how does this cause the vacant globin subunits to switch to R-state at the same time (3 marks)

Each O_2 that binds applies an opposing force on Fe^{2+}; and each O2 increases the probability of switch to R state

When the switch occurs, the whole hemoglobin molecule changes state in all its subunits simultaneously (MWC model)

Hemoglobin switches state by a single global change, rotation of a1b1 relative to a2b2, which changes the interactions between neighbouring globins

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22. Explain the metabolic logic suggested by each of the following allosteric regulators:
Example:
CTP is a negative regulator of ATCase because CTP is a representative pyrimidine and if CTP concentration is high, there is no need for ATCase to begin the synthesis of more pyrimidines.

ATP is a positive regulator of ATCase because (3 marks each)
High ATP is suggestive of active cell growth with DNA and RNA synthesis
ATP is a representative purine,
excess of purine over pyrimidine suggests that pyrimidine synthesis is needed

AMP is a positive regulator of glycogen phosphorylase b because
AMP is sensitive indicator of the cell's energy status
[AMP] rises when ATP is consumed
AMP signals that glycogen phosphorylase should release glucose phosphates from glycogen to supply the glycolysis pathway

Acetyl CoA is a positive regulator of pyruvate carboxylase because
Presence of acetyl CoA represents capacity to make ATP via TCA cycle
Presence of acetyl CoA suggest sources other than glycolysis (e.g. b-oxidation) are providing it
Therefore gluconeogenesis can be supported
or
Accumulating acetyl CoA suggests that some oxaloacetate should be made to support the action of citrate synthase

Citrate is a positive regulator of fructose-1,6-bisphosphatase because
Accumulation of citrate indicates that more substrate is available in TCA cycle than current energy needs require.
The cell can use surplus substrate and ATP to invest in gluconeogenesis
Fructose-1,6-bisphosphatase is a key regulated step in gluconeogenesis

23. Fructose-2,6-bisphosphate promotes glycolysis and inhibits gluconeogenesis.

What enzyme makes fructose-2,6-bisphosphate?_ **Phosphofructokinase 2, PFK2**____
1 mark

How is it regulated so that protein kinase A activates gluconeogenesis in liver, but activates glycolysis in muscle?

PFK2 is half of a bifunctional enzyme that also contains fructose-2,6-bisphosphatase

When liver isozyme is phosphorylated by PKA, it is activated in the FBPase2 half, so Fru-2,6-bisP breaks down, allowing gluconeogenesis to proceed.

When the muscle isozyme is phosphorylated by PKA, it is activated in the PFK half, so Fru-2,6-bisP is made and signals for glycolysis to proceed

3 marks

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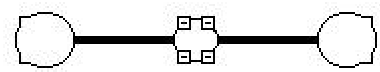
24. The diagram on the left represents a **fibrinogen** molecule



a) How are the subunits arranged in this molecule (2 marks)

Option 1: describe the components

6 subunits, (Aa ,Bb,g)$_2$ arranged symmetrically about the centre

Option 2: describe the layout

Triple helical coils meeting in a central knot at the N-terminal end, C-terminal globular domains at the extreme end

b) What is the action of thrombin on fibrinogen, and how does this allow fibrin to polymerize into fibres? (4 marks)

Thrombin is a highly selective serine protease, and cleaves fibrinogen to remove fibrinopeptides A and B

Fibrinopeptides A and B are rich in negative amino acids

This exposes positive charge sites in the central knot of fibrin, which is now composed of (abg)$_2$

Fibrin molecules can now build fibrous polymers because the positive central knot binds negative globular ends in a staggered or brick-like pattern.

c) What modified amino acid is found in prothrombin and other clotting factors? (1 mark)

g-carboxyglutamate

d) What vitamin is necessary for effective blood clotting _______Vit K___________ (1 mark)

e) What special behaviour is associated with this amino acid, and how does it promote activation of prothrombin on negative phospholipid or glass surfaces? (3 marks)

g-Carboxyglutamate has a double negative charge which binds Ca^{2+} much more strongly than normal Glu or Asp

Ca^{2+} can bridge between negative prothrombin and other clotting factor proenzymes and negative phospholipid surfaces (Glass mimics the effect of phospholipid)

Binding to the surface provides a local concentration of clotting factors allowing the cascade to start whereas in blood they are too widely dispersed

f) What inhibitor prevents accidental activation of traces of thrombin and other clotting factors from setting off the whole cascade?

______**Antithrombin III**_______________ (1mark)