

Name _____

Student number _____

Answer questions 1-20 on the computer scoring sheet.

Value 2 marks each

1. Which hemoglobin form is expressed during **months 2-9 of pregnancy**?
- A) $\zeta\zeta\beta\beta$ B) $\epsilon\epsilon\beta\beta$ **C) **aagg****
D) $\alpha\alpha\delta\delta$ E) $\epsilon\epsilon\gamma\gamma$ 1) A B C D E
2. Which of the following circumstances **allows survival in cases of β -thalassemia** where both parents' β -globin genes are defective?
- A) A $\beta\beta\beta\beta$ hemoglobin variant is produced
B) A $\alpha\alpha\alpha\alpha$ hemoglobin variant is produced
C) Myoglobin appears in blood to replace the defective hemoglobin
D) Fetal hemoglobin continues to be expressed after birth
E) O_2 binds to free heme- Fe^{2+} in blood 2) A B C D E
3. What are the characteristics of **hemoglobin S** that forms in **sickle cell anemia**?
- A) It does not bind O_2 B) It does not show allosteric behaviour
C) It binds O_2 too tightly D) It polymerizes into fibres when it binds O_2
E) It polymerizes into fibres when it is deoxygenated 3) A B C D E
4. Which of the following statements about the **effect of pH** on hemoglobin is **not correct**?
- A) Higher pH promotes R state in hemoglobin
B) Higher pH promotes deprotonation of His HC3 side chain
C) Higher pH in peripheral tissues promotes O_2 release
D) Higher pH causes the sigmoidal O_2 binding curve to shift leftwards
E) Higher pH results in a lower P_{50} for O_2 4) A B C D E
5. Which of the following **correctly describes how CO_2 interacts** with hemoglobin?
- A) CO_2 binds to heme Fe^{2+} B) CO_2 binds to His E7
C) CO_2 binds to His F8 **D) CO_2 binds to the N-terminal of α -globin**
E) CO_2 binds to heme Fe^{3+} 5) A B C D E
6. Which of the following statements about **Heme, Fe^{3+} and O_2 binding** is **true**?
- A) Heme- Fe^{3+} binds H_2O in preference to O_2**
B) Heme- Fe^{3+} is undesirable in myoglobin because it binds O_2 too tightly
C) Heme can't bind Fe^{3+}
D) Oxidation to heme- Fe^{3+} is part of the process for reversible O_2 binding
E) Heme- Fe^{3+} binds CO_2 6) A B C D E

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7. Which of the following statements about phosphorylase *b* kinase is **not correct**?
- A) Phosphorylase *b* kinase can be activated by binding Ca^{2+}
B) Phosphorylase *b* kinase can be activated by binding cyclic AMP
C) Phosphorylase *b* kinase catalytic subunit resembles protein kinase A catalytic subunit
D) Phosphorylase *b* kinase is inactivated by an autoinhibitory loop on its β subunit
E) Phosphorylase *b* kinase can be activated when protein kinase A phosphorylates its α and β subunits
7) A B C D E
8. Which of the following statements about **regulation of cyclin dependent kinase** is **not correct**?
- A) Cyclin must bind before CDK can be activated
B) A tyrosine near the ATP substrate site must be phosphorylated for activity
C) Cyclin kinase inhibitors inactivate CDK by blocking the protein substrate site
D) Activating cyclin is destroyed by proteolysis when the cell cycle phase is complete
E) Thr 160 must be phosphorylated for peak activity
8) A B C D E
9. Which of the processes for **activation of pancreatic proenzymes** is **not correct**?
- A) Enteropeptidase can activate trypsinogen
B) Trypsin can activate trypsinogen
C) Chymotrypsin can activate trypsinogen
D) Trypsin can activate chymotrypsinogen
E) Trypsin can activate Procarboxypeptidase
9) A B C D E
10. Which of the following **correctly describes** the role of **tissue plasminogen activator**?
- A) promotes clotting by activating fibrinogen
B) promotes clotting by activating prothrombin
C) prevents clotting by binding to fibrinogen
D) prevents clotting by binding to prothrombin
E) promotes the dissolution of clots
10) A B C D E
11. Which of the following factors is **common to the extrinsic and intrinsic** blood clotting pathways?
- A) Factor VIII
B) Factor IX
C) Factor X
D) Factor XI
E) Factor XII
11) A B C D E
12. What is the mechanism by which **caffeine stimulates glycogen breakdown**?
- A) Caffeine inhibits breakdown of cyclic AMP**
B) Caffeine is an allosteric activator of glycogen phosphorylase
C) Caffeine inhibits phosphoprotein phosphatase
D) Caffeine binds to protein kinase A
E) Caffeine stimulates production of cyclic AMP
12) A B C D E
13. Which of the following is responsible for activating **Protein kinase A**?
- A) Cyclic AMP binds to C subunits of protein kinase A
B) Cyclic AMP becomes available as phosphate donor
C) Cyclic AMP is hydrolyzed to 5'-AMP
D) Cyclic AMP binds to R subunits of protein kinase A
E) The proenzyme form is cut by proteolysis
13) A B C D E

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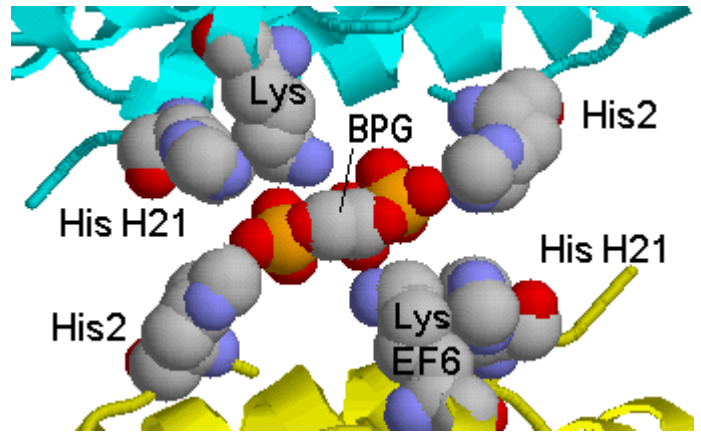
21. The figure shows the ligand BPG bound in hemoglobin.

What does BPG stand for?

____2,3-bisphosphoglycerate____
(1 mark)

Which globin subunits does the BPG bind to?

____β1 and β2____
(1 mark)



What happens to O_2 affinity of hemoglobin in the absence of BPG?

2 marks

Affinity increases (1) to $P_{50} = 0.26$ kPa or to be similar to myoglobin (1)

The graph below shows how myoglobin binds O_2 . Add a curve for hemoglobin+BPG (2 marks), and use it to explain why BPG is beneficial to the function of hemoglobin (3 marks)

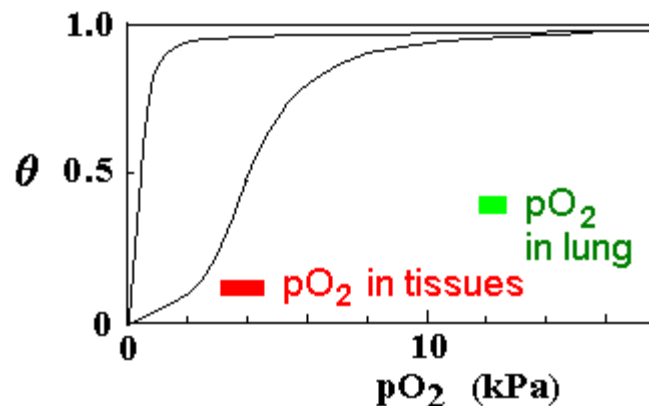
graph line: reasonable sigmoidal shape (1)

and reach near saturation around lung pO_2 (1)

BPG can only bind to hemoglobin in T state

Its presence shifts the $T \rightleftharpoons R$ equilibrium in favour of T, so P_{50} is higher

Reduced affinity for O_2 allows for better O_2 release at pO_2 values typical of peripheral tissues



In hemoglobin F, His H21 is replaced by Ser. How does this affect the binding of BPG, and why is this important for fetal hemoglobins? (3 marks)

Histidine H21 contributes partial positive charge but serine is neutral, and this decreases the electrostatic attraction for highly negative BPG

Decreased binding of BPG disfavours T state, so O_2 affinity of HbF is greater than HbA

Higher O_2 binding affinity of fetal hemoglobin allows for transfer of O_2 from the maternal blood to the fetus

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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 negative regulator of fructose-1,6-bisphosphatase because

AMP is sensitive indicator of the cell's energy status

[AMP] rises when ATP is consumed

AMP signals that fructose-1,6-bisphosphatase should halt gluconeogenesis to conserve ATP

Acetyl CoA is a negative regulator of pyruvate kinase because

Presence of acetyl CoA represents capacity to make ATP via TCA cycle

Presence of acetyl CoA suggest sources other than glycolysis (e.g. β -oxidation) are providing it

Therefore glucolysis should be stopped to conserve glucose

Glucose-6-phosphate is a negative regulator of glycogen phosphorylase because

Glucose-6-phosphate is an end product of glycogen breakdown

If glucose-6-phosphate is accumulating, there may be another source providing it

Glycogen breakdown can be halted to conserve glycogen

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?

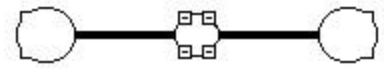
PFK2 is half of a bifunctional enzyme that also contains fructose-2,6-bisphosphatase

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

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 Ca²⁺ much more strongly than normal Glu or Asp

Ca²⁺ 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)