2018 Cell Signalling STQ MS

2018 / H2 / ACJC PRELIM / P2 Q2

1 Fig. 2.1 shows the activation of a G-protein linked receptor (GPLR) found in the cell surface membrane upon binding of a drug, salbutamol. Salbutamol is often used in the treatment of asthma – a long-term condition which narrows the airways in the lungs. The G protein consists of three subunits - α, β, and γ.

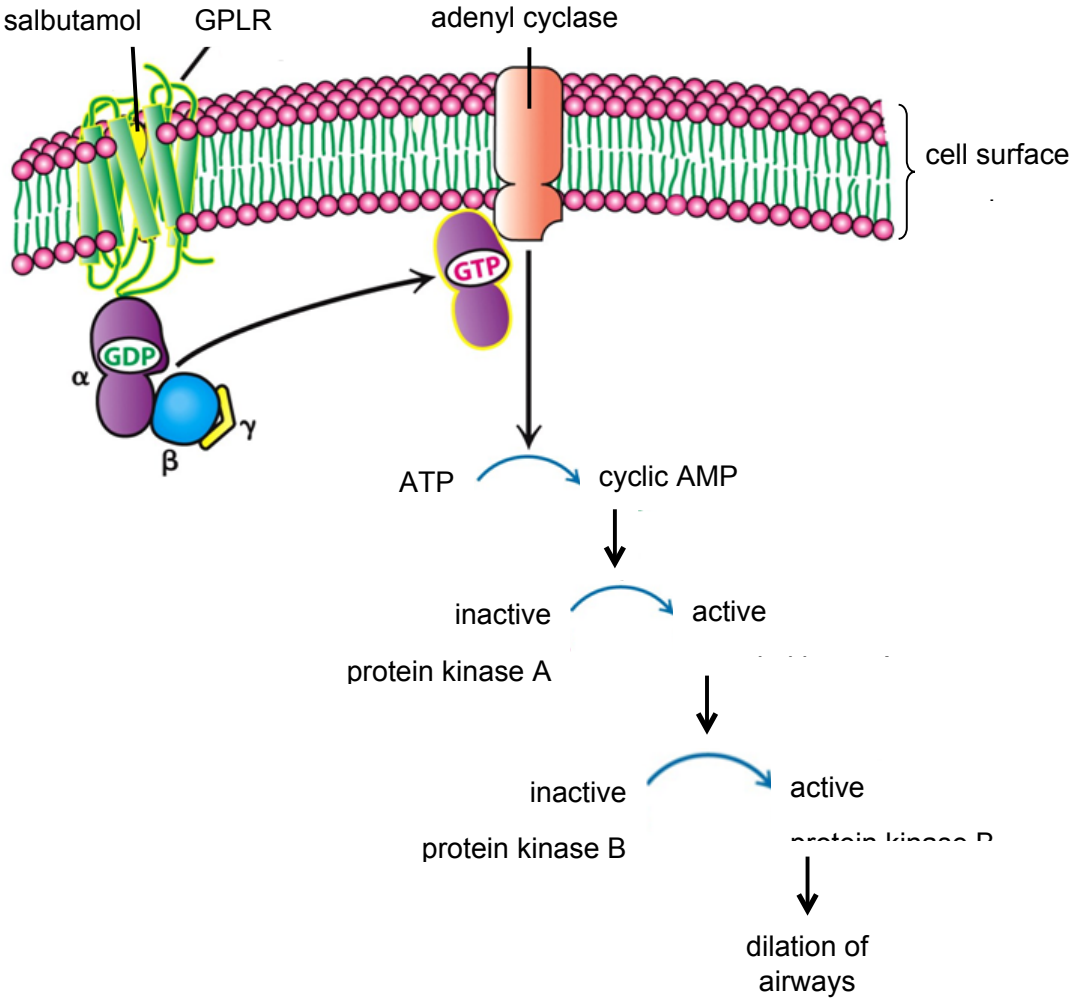

Fig. 2.1

(a) Describe how GPLR is held within the cell surface membrane.

1. **Hydrophobic interactions occur between the hydrophobic core/hydrocarbon tails of phospholipid bilayer and hydrophobic R groups of amino acid residues of GPLR;**

2. **Hydrogen/ionic bonds formed between charged/ hydrophilic phosphate heads of phospholipids and hydrophilic R groups of amino acids in cytoplasmic +**

extracellular regions of GPLR; [2]

(b) With reference to Fig. 2.1, describe how the use of salbutamol can relieve symptoms of asthma.

1. **Binding of salbutamol to a specific/complementary binding site of GPLR result in conformational change of receptor;**
2. **Activated GPLR activates G protein, where GTP replaces GDP;**
3. **α subunit dissociates from βγ subunits;**
4. **α subunit binds to and activates adenyl cyclase (at the membrane), which catalyses the conversion of ATP to cAMP;**
5. **cAMP act as second messengers and activates protein kinase A;**
6. **trigger a phosphorylation cascade resulting in amplification of signal, causing to dilation of airways;**

[Total: 8]

(c) There are many different types of receptors used by a cell to transduce extracellular signals. Some are located on the cell surface membrane while others are located within the cell.

Explain why some receptors are found on the cell surface membrane while others are found within the cell.

1. **Ligands which are lipid-soluble/hydrophobic/non-polar bind to specific nuclear receptors within the cell;**
2. **Ligands which are not lipid-soluble/hydrophilic/charged/polar bind to specific receptors on the membrane;**
3. **Ref to size;**

[2]

[4]

2018 / H2 / DHS PRELIM / P2 Q3

Question 2

(a)
A

Ligand IGF1 binds to the receptor tyrosine kinase. The receptor cross-phosphorylates each other and becomes activated;

PI 3-kinase binds to the phosphorylated region of receptor tyrosine kinase and becomes activated.

Activated PI 3-kinase phosphorylates and activates $PI(4,5)P_2$;

B

Phosphorylated $PI(4,5)P_2$ / $PI(3,4,5)P_3$ serves as a docking site at the cell surface membrane. PDK1 and Akt binds to the $PI(4,5)P_3$.;

Akt is phosphorylated by activated PDK1 and mTOR. Akt becomes activated and dissociates from $PI(3,4,5)P_3$ to phosphorylate Bad / causes Bad to bind to 14-3-3 protein;

(b) (i)

PI 3-kinase is mutated to become locked in the active state / resistant to phosphatases catalysis;

Activity of PI 3-kinase increases / pathway always switched on;

(b) (ii)

Bad protein is mutated such that the conformation of active site involved in binding is changed / unable to bind to apoptosis inhibitory protein;

Bad protein is mutated such that it is able to bind with 14-3-3 protein without phosphorylation / permanently;

2018 / H2 / EJC PRELIM / P2 Q7

3 Fig. 7.1 shows a CREB (cAMP response element binding) signalling pathway. This pathway is triggered when ligand X binds to a receptor at the cell membrane.

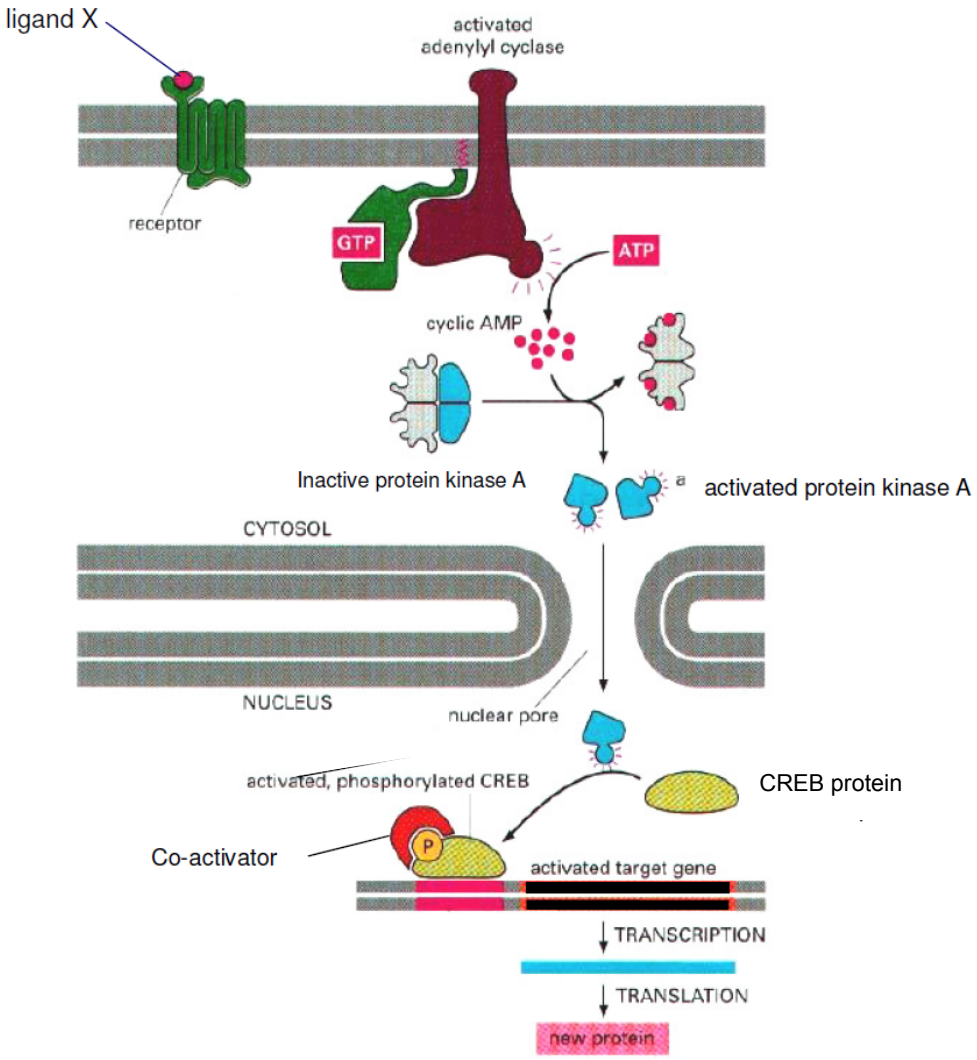

Fig. 7.1

(a) With reference to Fig. 7.1,

(i) Describe precisely the structure of the G protein coupled receptor and explain how the described structure enables it to perform its function.

……

……

……

……[2]

1. **GPCR is a receptor protein with seven transmembrane domains, consisting of hydrophobic regions forming hydrophobic interactions with the hydrophobic fatty acid tails/nhydrophobic core of the phospholipid bilayer;**
2. **Allows GPCR to be embedded on the cell surface membrane to allow it bind/ interact with hydrophilic/ polar/ large/ charged ligand;**

OR

3. **GPCR has an extracellular ligand-binding site that is complementary in shape and charge to the ligand allowing ligand to bind**
4. **to induce conformational change in intracellular domain of receptor leading to signal transduction;**

OR

5. **GPCR has an intracellular domain that associates with a G-protein;**
6. **Change in conformation of intracellular domain of receptor leading to signal transduction;**

(ii) Describe how protein kinase A (PKA) is activated.

……

……

……

……..[2]

1. **cAMP binds to 2 subunits of inactive protein kinase A;**
2. **the remaining 2 subunits dissociate and become activated protein kinase A;**

(iii) State the role of PKA in this signaling pathway?

……

……..[1]

1. **To phosphorylate the CREB protein so that co-activator can bind to it.**

(b) CREB is an activator protein that binds to its specific control element to upregulate the transcription of the target gene.

Explain how an activator protein like CREB can upregulate transcription of a gene.

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……

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……

……

……[3]

1. **CREB will bind to its enhancer on DNA;**
2. **causing the spacer DNA between the promoter of the gene and enhancer to bend OR**
   Recruit histone acetylase / chromatin remodelling complex to decondense chromatin;
3. **Thus promoting the assembly of RNA polymerase and general transcription factors at the promoter to form transcription initiation complex;**

(c) CREB is known to be involved in other signaling pathways. With reference to Fig. 7.1 or otherwise, suggest how it is possible for CREB to bind to other control elements so as to regulate the transcription of different genes.

……

……[1]

1. **CREB protein can be phosphorylated at different sites by PKA, leading to different conformation changes that allow CREB to bind to different control elements;**

2. **Different co-activators may be recruited and bind to CREB, leading to different conformation changes that allow CREB to bind to different control elements;**

(any one)

[Total: 9]

2018 / H2 / MJC PRELIM / P2 Q6

QUESTION 4

STAT proteins are cytoplasmic transcription factors that play important roles in the development and differentiation of many cell types. Upon external stimulation, STAT protein is activated from its inactive form and binds to another activated STAT protein to form a dimer. This protein dimer then translocates to the nucleus and regulates the expression of other genes as shown in Fig. 6.1.

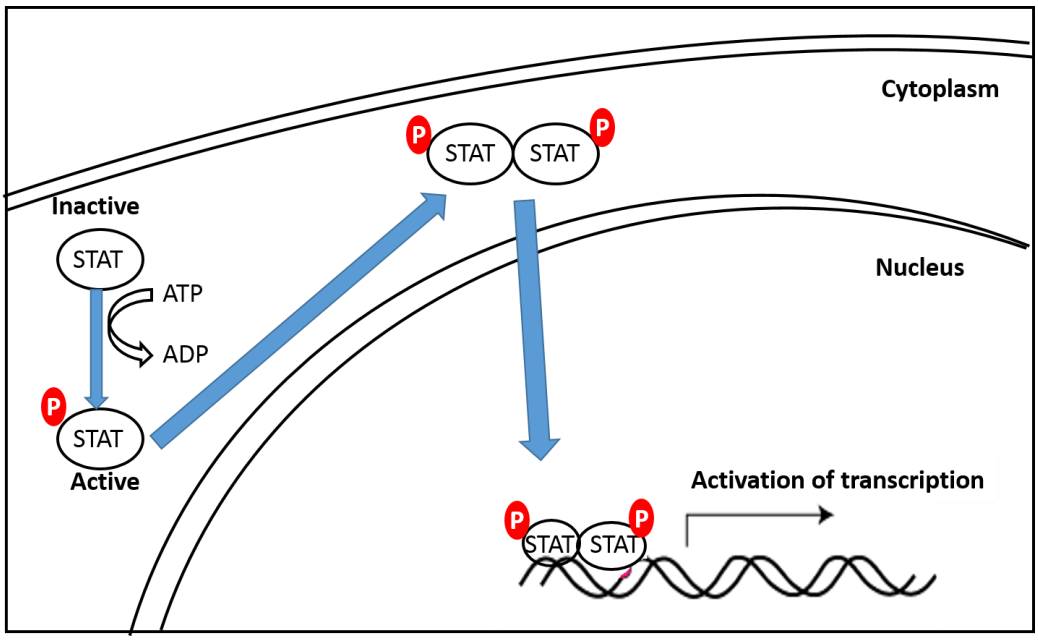

Fig. 6.1

(a) With reference to Fig. 6.1,

(i) explain how the inactive STAT protein is converted to its active form. [2]

Via **Post-Translational modification / phosphorylation**

ATP is hydrolysed to **donate a phosphate group** to the inactive STAT to form an active STAT protein.

(ii) besides converting the inactive form of STAT protein to its active form, describe how the level of the inactive STAT protein may be controlled after its production. [2]

These inactive forms of STAT may be **tagged with ubiquitin** proteins which are recognized by and **degraded in proteasomes**

This **decreases concentration / amount** of STAT

STAT5 gene, a member of the *STAT* family, is widely expressed in hematopoietic stem cells (HSC) to regulate the self-renewal and differentiation of the stem cells.

Fig. 6.2 shows the differentiation of HSC leading to the formation of different cell types such as T cell and B cell.

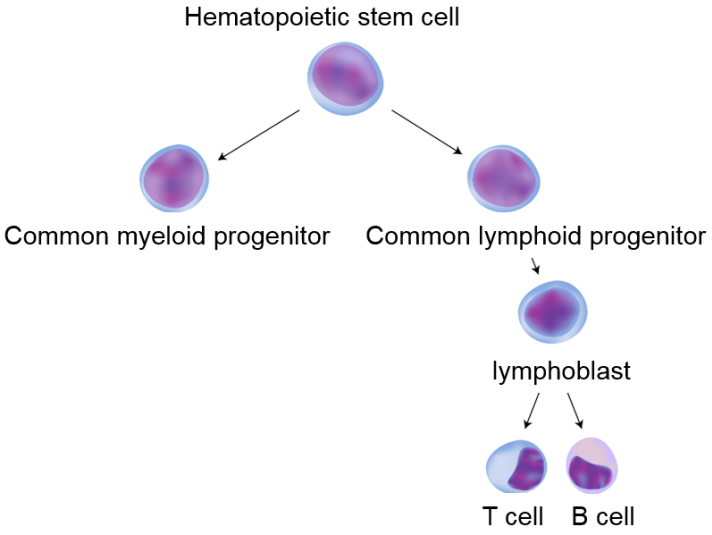

Fig. 6.2

(b) Explain how the different cell types such as T cell and B cell can arise from a single hematopoietic stem cell. [3]

Idea of **differential gene expression** occurred during differentiation.

The **specific combination of activators** present in the cells are **different.** They bind to their respective **enhancers** to up-regulate transcription of T cell -specific genes and B cell-specific genes respectively / idea of repressors and silencers
Or

Idea of Different sets of cell type specific genes were switched on/off by DNA methylation / histone deacetylation / histone methylation….

Different sets of proteins are synthesized, causing the two cells to have different structures and hence functions.

(c) In humans there are different forms of STAT5 protein, each plays a slightly different role in different cell types.

Explain how the same *STAT5* gene can produce different forms of STAT5 protein. [2]

Alternative RNA splicing

Different spliceosomes in different cell types bind to specific **splicing sites** in the introns of pre-mRNA

Different combinations of exons are **spliced** together to form three different mature mRNA hence different protein forms of STAT5 protein.

[Total: 9]

2018 / H2 / NJC PRELIM / P2 Q2

5 In an experiment to investigate the effect of insulin on glucose uptake by muscle cells, the concentration of free glucose inside muscle cells was measured with respect to the extracellular glucose concentration, in the presence of insulin (labelled as insulin) and in the absence of insulin (labelled as control).

Fig. 2.1 shows the results of the experiment.

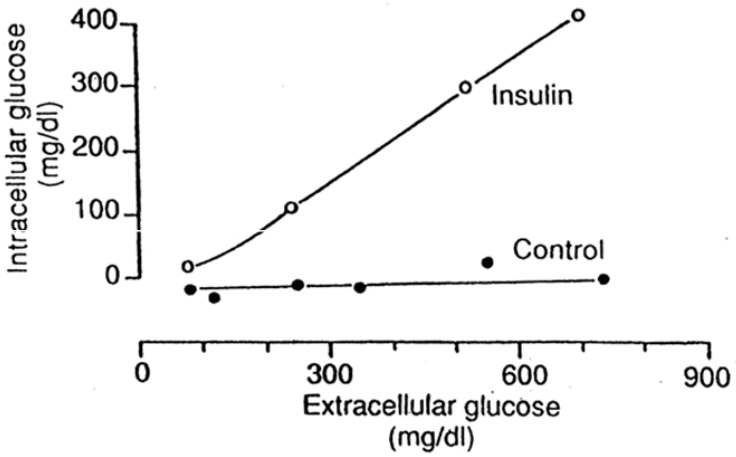

Fig. 2.1

(a) With reference to Fig. 2.1, describe the effect of insulin on glucose uptake by muscle cells.

1. **Insulin leads to an increase in glucose uptake / intracellular glucose concentration in the muscle cells;**
2. **In the absence of insulin, intracellular glucose concentration remains constant at about 0 mg/dl as extracellular glucose concentration increases from 78 (70 – 80) to 733 (720 – 740) mg/dl;**
3. **In the presence of insulin, intracellular glucose concentration increases from 22 (10 – 30) to about 400 (400 – 420) mg/dl as extracellular glucose concentration increases from 78 (70 – 80) to about 700 (690 – 710) mg/dl;**

[3]

(b) **(i)** Name the type of receptor that insulin binds to on the muscle cell.

Receptor tyrosine kinase / Tyrosine kinase receptor;
(Reject: Insulin receptor; RTK) [1]

(ii) Explain how the binding of insulin to its receptor could result in the effect shown in Fig. 2.1.

1. **The binding of insulin to its receptor would induce a conformational change in the receptor, bringing the two internal tyrosine kinase domains closer together;**
   (Reject: cause receptor dimerisation)
2. **Contact between the two adjacent tails of the receptor would activate their tyrosine kinase function, leading to cross-phosphorylation / autophosphorylation of the tyrosine residues present in the tails of the receptor;**
3. **The fully activated receptor would trigger the assembly of adaptor proteins on the receptor tails, which will further recruit and activate other downstream relay molecules via phosphorylation;**
4. **More glucose transporters (GLUT4) would become embedded in the plasma membrane, increasing the glucose uptake / intracellular glucose concentration in the muscle cells;**

[4]

(c) Suggest how the effect of insulin on glucose uptake by muscle cells could be terminated.

1. **degradation of insulin by enzymes;**
2. **endocytosis of insulin-RTK / ligand-receptor complex;**
3. **increase in the activity of phosphatases / enzymes that dephosphorylate proteins;**

[1]

[Total: 9]

2018 / H2 / PJC PRELIM / P2 Q9

6 Fig. 9.1 shows the glucagon signalling pathway.

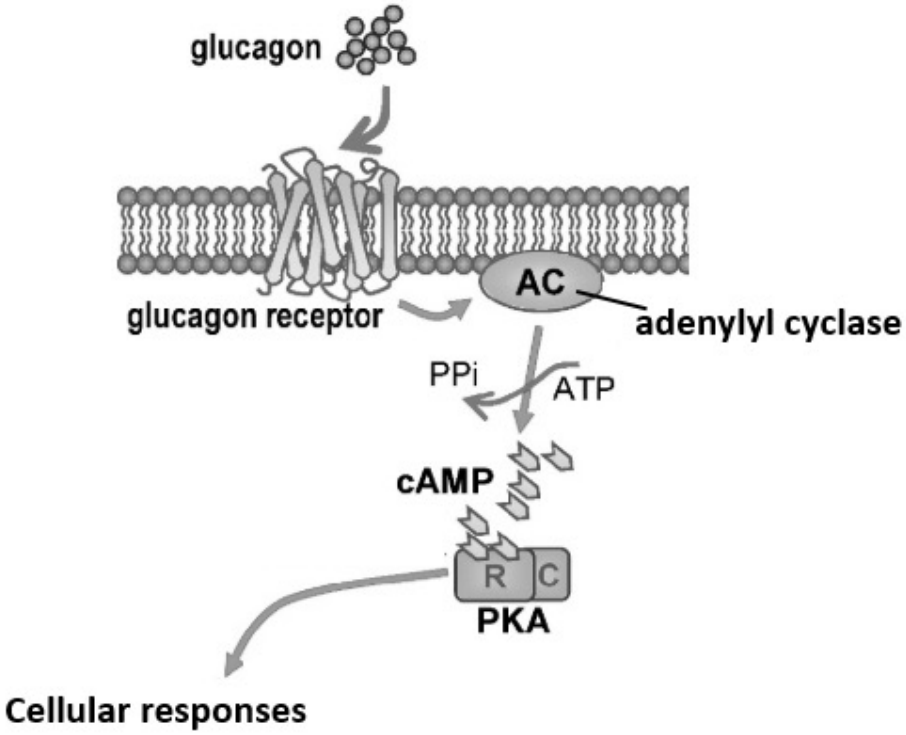

Fig. 9.1

(a) In humans, in which types of cells are glucagon receptors mainly found? [1]

Liver cells;;
A! Kidney cells

(b) Describe how the glucagon receptor transmits information from the external environment to activate adenylyl cyclase inside of the cell. [3]

a. The ligand, glucagon, binds to the GPCR, which is linked to a G-protein and triggers conformational changes in the GPCR, exposing the cytoplasmic domain of the GPCR;;
b. G protein binds to GPCR and exchanges GDP for GTP, and GTP-bound G protein becomes active;;
c. G protein dissociates from the receptor, (moves along the cell surface membrane), and binds to adenylyl cyclase to activate it.

[Turn over

(c) Describe two cellular responses resulting from the cell signalling pathway shown in Fig. 9.1. [2]

a. Glycogenolysis / conversion of stored glycogen to glucose, releasing this glucose into the bloodstream;;
b. Stops the liver cells from consuming glucose, helping more glucose to remain in the bloodstream;;
c. Gluconeogenesis / production of glucose from amino acids or other sources;;

max. 2

(d) In signal transduction pathways, how can the response of the target cell to a hormone be amplified? [2]

a. Amplification occurs at the signal transduction stage, where the binding of one ligand molecule (at the receptor) activates relay molecules which in turn activate an increasing number of downstream relay molecules;;
b. As such, the number of activated relay molecules is much higher than the preceding step;;
c. Signal amplification can be achieved via phosphorylation cascades, e.g. activation or the production of second messengers;;
d. Signal amplification requires the activated relay molecules or second messengers to remain in an active form long enough to activate a high number of downstream molecules;;

max. 2

[Total: 8]

2018 / H2 / SAJC PRELIM / P2 Q1

QUESTION 7

Fig 1.1 shows the structure of a G-protein-linked receptor (GPLR) from a cross-section of the plasma membrane.

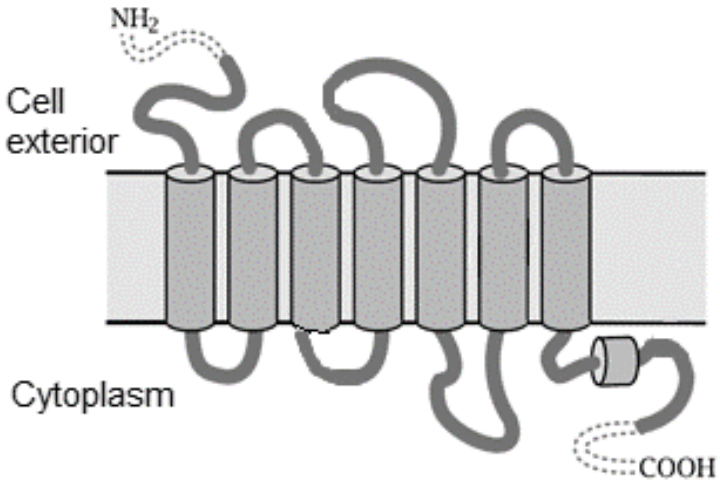

Fig 1.1

(a) With reference to **Fig 1.1**, describe the significance of R groups to the structure and function of a GPLR.

…..…….. [5]

1. Ref. seven **transmembrane domains/segments**, consisting of **amino acids with hydrophobic R groups**
2. that have <u>hydrophobic interactions</u> with **hydrophobic core** of plasma membrane;
3. **hydrophilic/polar** R groups of amino acids interacting with hydrophilic **phosphate heads** / **aqueous** medium;
4. ref. hydrogen bonds / ionic bonds (Note: hydrophilic interactions are vague)

5. ref. **extracellular** segment/domain/binding site which binds to **signal molecules /ligand**
6. ref. **intracellular/cytoplasmic** segment/domain/binding site which binds to <u>G-protein</u>
7. Ref. R groups of amino acids at binding site forming temporary interactions / providing complementary 3D conformation for signal molecules/G protein to bind

(b) The GPLRs make up the largest family of cell surface receptors. Outline the route taken by the GPLR after its synthesis to its final location in the plasma membrane.

…….. [4]

1. Newly synthesised polypeptide enters the rough endoplasmic reticulum (rER**)** and **folds into its native / 3-dimensional conformation**
2. Protein undergoes **chemical / post-translational modification** (where short carbohydrate chains are added to these proteins (glycosylation))
3. ref. GPLR being packaged into **transport vesicles** which **buds off the rER** and **fuse with** cis **face of the Golgi body**
4. where **further chemical / post-translational modification** of the protein occurs.
5. Modified proteins packaged into **secretory vesicles** which **bud off the** trans **face** of the Golgi body.
6. Secretory vesicles move to and **fuse with the cell surface membrane** / plasma membrane, GPLR embedded within plasma membrane;
7. Ref. movement of vesicles on cytoskeleton / microtubules involving ATP hydrolysis

GPLRs are found to be closely associated with a type of G protein called K-Ras in the cell signaling pathways.

Fig. 1.2 is a simplified diagram showing the normal roles of GPLR and K-Ras in the RAS/MARK signaling pathway.

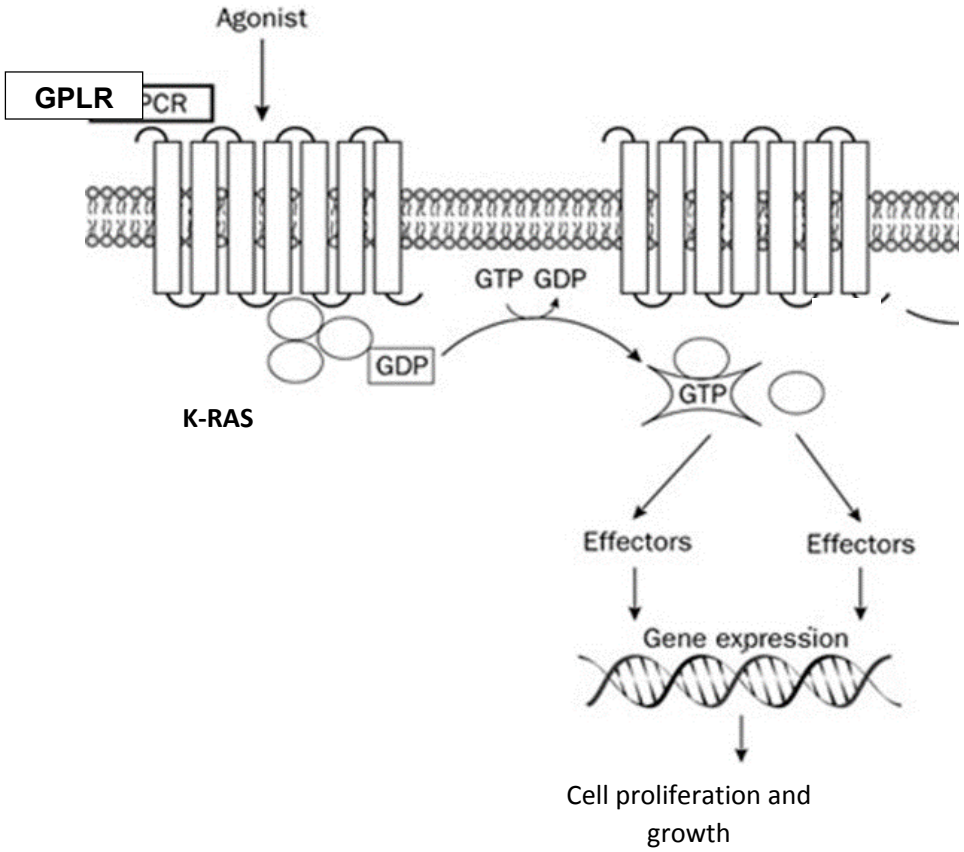

Fig. 1.2

(c) Assuming that the effectors (in **Fig. 1.2**) in the transduction pathways function normally, explain how a mutation can lead to the formation of tumours in cancer.

…….. [4]

1. (gain of function) Mutation in the K-Ras gene
2. ref. K-Ras protein functions as a GTPase enzyme;
3. Mutated K-Ras protein unable to hydrolyse/convert GTP to GDP / mutated K-Ras continuously/constitutively bound to GTP; ref. mutated K-Ras protein constitutively activated/switched on
4. activating/switching on downstream **transduction** pathways / ref. expression of genes; that lead to continuous cell growth and division;
5. Ref. accumulations of other mutations / 1 example e.g. tumour suppressor genes / other proto-oncogene mutations

Or

1. Mutation in the GPLR gene
2. Mutated GPLR unable to hydrolyse ligand / ligand continuously bound to mutated GPLR / doesn't require ligand for activation;
3. GPLR continuously activated to (expose K-Ras binding domain to) bind to G-protein; K-Ras protein continuously activated/switched on
4. activating/switching on downstream **transduction** pathways / ref. expression of genes that lead to continuous **cell growth and division;**
5. Ref. accumulations of other mutations + 1 example e.g. tumour suppressor genes / other proto-oncogene mutations

2018 / H2 / VJC PRELIM / P2 Q6

8 Some hormones circulating in the blood are able to trigger transcription within a cell, even though they are unable to enter the cell. Phosphatases and kinases then take part in cell activities that eventually result in genes switching on and transcription beginning.

(a) Suggest why the hormones, referred to in the passage, are unable to enter the cell. [2]

Hormones are protein / peptide;
Too large to cross membrane;
Hydrophilic / water soluble; A not, hydrophobic / lipid soluble
Unable to pass through hydrophobic core / AW, of phospholipid bilayer;

(b) Use the information in the passage to outline the process of cell signalling. [3]

Chemicals / signalling molecules released are circulating hormones;;

Hormones bind to cell surface receptors on target cells/ cells where transcription is triggered;;
Signal is transduced into the cell / reference to extracellular signals are converted into intracellular signals;;
Action of kinases and phosphatases (within the cell) lead to (specific) response;;

(c) Explain the role of the following in cell signalling.

(i) Phosphatases [2]

Enzymes that catalyse the removal of phosphate groups from proteins, (must have);;
Making them inactive to end the signal transmission;;
Making the proteins in the cell signalling pathway available for reuse;;

(ii) Kinases [2]

Enzymes that catalyse the addition of phosphate groups from ATP to a protein, causing conformation change and the activation of the protein;;
When a kinase is activated, it phosphorylates the next kinase which continues sequentially down the pathway in a phosphorylation cascade;;