Cell Biology

Cell Signalling Pathway :-

Q) What are the main function of cell signalling pathway?

(A) (i) Recognition of the stimulus at the outer surface of the plasma-membrane by a specific-receptor embedded in the membrane.
(ii) Transfer of a signal across the plasma-membrane to its cytoplasmic surface.
(iii) Transmission of the signal to specific effector molecules on the inner surface of the membrane or within the cytoplasm that trigger the cell's response. Depending on type of cell & stimulus; the response may involve a change in gene expression, and alteration of the activity of metabolic enzymes, a reconfiguration of cytoskeleton, a change in ion permeability, activation of DNA synthesis, or even the death of the cell.
(iv) Cessation of the response as a result of the destruction or inactivation of the signalling molecules combined with a decrease in the level of the extracellular stimulus.

Some signal molecules giving cells interior signal :-

(1) Steroid hormones, act on target-cells by diffusing through the plasma-membrane & binding to a cytoplasmic receptor.
(2) Another intercellular messenger called nitric oxide, passes through the plasma-membrane, passed through rather than acting at the cell-surface.
(3) A few extracellular agents can evoke their response directly without having to initiate a signal inside the cell.

E.g Neurotransmitter Acetylcoline acts by such a mechanism when it binds to a receptor on a skeletal muscle cell, opening an ion-channel, that lies

Cyclic GMP pathway :-

(ii) The cGMP is also an important secondary messenger in animal cells. ~~Although~~

cGMP is formed → from GTP by guanylyl cyclase and degraded by GMP by a phosphodiesterase. The action of cGMP ~~protn~~ is frequently mediated by activation of a cGMP dependent protein Kinase. The best characterised role of cGMP is in the vertebrate, where it serves as the secondary-messenger, responsible for converting the visual signals, received as light to nerve impulses. The photoreceptors in rod cells of retina is a G-protein coupled receptors called rhodopsins, which is activated as a result of the absorption of light by the associated small molecules which then isomerises to all ~~trans~~ trans retinal molecules, inducing a conformational change, in the rhodopsin-protein. Rhodopsin then activates the G-protein transducin and the α-submit of transducin stimulates the activity of c.GMP phosphodiesterase, leading to the decrease in the intracellular level of c.GMP. (Fig 12/03)

(iii) MAP-Kinase pathway :- MAP-kinase pathway refers to a cascade of protein kinases that are highly conserved in evolution and play central roles in signal transduction in all eukaryotic cells, ranging from yeast to humans.

- The central elements in the pathway are a family of protein-Serine/threonine kinases called the MAP kinases that are activated in response to variety of growth factor and other signalling molecules. The best characterised forms of MAP kinase in mammalian-cells, belong to the E.R.K (Extracellular Signal Regulated kinase) family. The E.R.K activation plays a central role in signalling cell proliferation induced by growth factors that act through either protein-tyrosine kinase OR G-protein coupled receptors. Activation of E.R.K. is mediated by two upstream protein-kinases which are coupled to growth factor receptors by a GTP-binding protein called Ras. Activation of Ras leads to - activation of the Raf protein — Serine/threonine kinase

Pathways of Intracellular Signal Transduction from Receptors :-

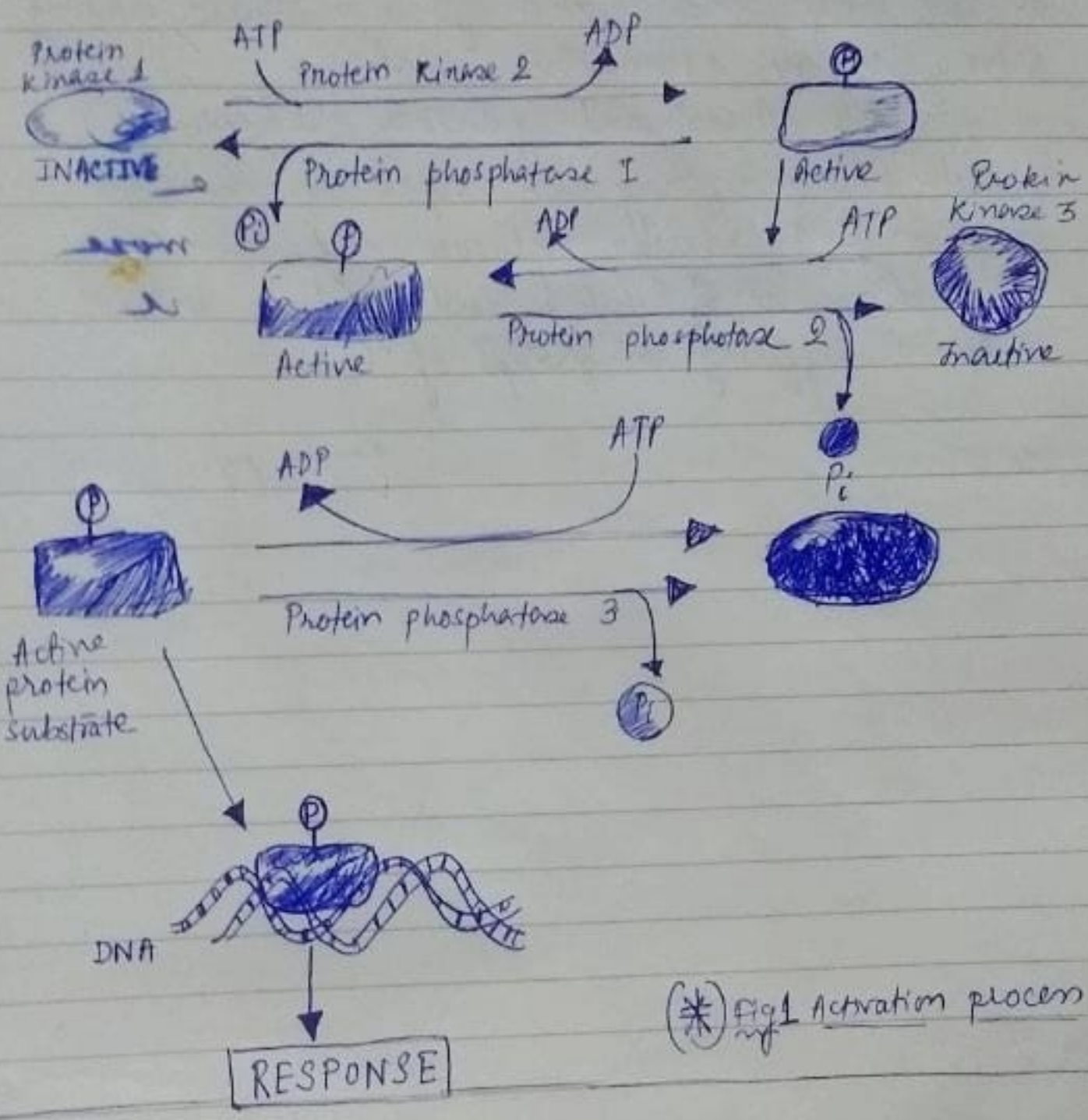
Most cell-surface receptors stimulate intracellular target enzymes, which maybe either directly linked OR indirectly coupled to receptors by G-proteins and in most cases a chain of reactions, transmits signals from the cell-surface to a variety of intracellular targets — proces called intra-cellular signal transduction :-

(1) The c.AMP pathway :- The cyclic AMP mediated signal is produced by the action of c.AMP dependent protein Kinase A. The regulation of glycogen-metabolism, protein-kinase A, phosphorylates to key target enzymes. The first is another protein-kinase, phosphorylase-kinase (PhK), which is phosphorylated and activated by protein kinase A. Protein kinase phosphorylates and activates glycogen phosphorylase which catalyses the breakdown of glycogen to glucose-1 phosphosphate. In addition, protein kinase A. phosphorylates the enzyme glycogen synthase which catalyses glycogen-synthesis.

Elevation of cAMP and activation of protein-kinase A thus blocks further glycogen-synthesis.

The chain of reactions leading from the epinephrine-receptor to glycogen-phosphorylase is the signal amplification process. where each mol. of epinephrine activates only a single receptor but each receptor may activate upto 100 molecules. of glycogen-synthase (G.S.) and molecule of glycogen-synthase then stimulate the enzymatic activity of adenylyl-cyclase, catalysing the synthesis of many molecules of cAMP.

3.) Guanine nucleotide - dissociation inhibitors (GDI's) :-
GDI's are proteins that inhibit release of a bound GDP from a G-protein, thus maintaining in the inactive GDP-bound state.



(*) Fig 1 Activation process.

exist in two interchangeable states : an active state that contains a bound GTP and an inactive states that contains a bound GDP

Although the difference in conformation may appear subtle, the active, GTP-bound protein is able to bind specific-proteins (ie, downstream targets) with which the GDP-bound proteins cannot interact. In most instances, binding of the GTP-bound proteins activates downstream target, allowing it to carry out a particular functions. Hydrolysis of bound GTP- causes the G-protein to revert to the inactive state, & it's dissociates from the downstream target.

The cyclicity of G-proteins b/w active & inactive states is aided by ~~accessory~~ accessory-proteins that bind to the G-proteins & regulate its activity. These accessory-proteins include,-

1. GTP-ase activating proteins (GAP's) Most G--proteins possess some capability to hydrolyse a bound GTP, but with capability is greatly accelerated by interaction with sp. GAP's. Because they stimulate hydrolysis of the bound GTP, which inactivates the G-protein, GAP's dramatically shorten the duration of G-protein mediated response.

2. Guanine nucleotide-exchange factors (GEF's)- An inactive G-proteins is converted by the active form when the bound GDP is replaced with a GTP, GEF's are proteins that bind to an inactivate G-proteins & stimulate dissociation of bound GDP. Once the GDP is released, the G-protein rapidly binds a GTP, which is present at relatively high concentrations in the cell, thereby activating the G-proteins.

within the receptor itself.

Basic characters of cell signalling system:-

① - The term cell-signalling describe the concept that a cell responds to a stimulus from its environment by relaying information to its internal-compartment.

② - In most cases, the stimulus is a molecule that has been secreted into the extracellular space by another cell but it may also originate from contact with another cell or a non-cellular substratum.

③ - Signal-transduction is a complex-process in which information passes along signalling pathways that consists of a series of distinct proteins which typically acts by altering the conformation of the subsequent proteins in the series, an event that activates or inhibits that protein.

④ This alterations in the confirmation of signalling proteins are usually accomplished by protein kinases & phosphatases. that add OR remove phosphate-groups from other proteins.

Fig-1

① Some of the kinases and phosphatases are soluble cytoplasmic proteins and others are integral membrane proteins.

⑤ ——> Some of this enzymes have numerous-proteins as their substrates whereas others phosphorylate OR dephosphorylate only a single protein substrate whereas, many of the protein substrates of these enzymes are other enzymes-are most often other kinases and phosphatases but the substrates also include ion channels, transcription-factors and other various types of regulatory subunits.

⑥ There is an involment of GTP binding proteins (i.e. G-proteins) as switches that in turn activates "ON OR OFF"

G-proteins can act as switches because they exists in two interchangeable states; an active-state cause they