SECTION A

Answer Multiple Choice questions
i) Which of the following is NOT true about hormone- b) hormones are released from exocrine gland

ii). One of the following is the Calcium –binding protein of the cell c) calmodulin

iii) Which of the following hormone is considered a glucocorticoid c) cortisol

iv) Which of the following is a steroid hormone a) testosterone

v) An enzyme that adds a phosphate functional group to amino acids is called a a) kinase

vi) Protein kinase A is a family of enzymes consists of c) two domain with small several β sheets and larger α helices

vii). Increase activity of phosphodiesterase in target cell would decrease its level of b) cAMP

viii). Find the odd one out from the following b) cAMP

ix) When action of two hormones are mediated by same signal transduction, it is c) synergistic action

x) A hormone that promotes gluconeogenesis in the liver is b) cortisol

SECTION B

a) Describe about the regulation of exocytosis following calcium channel.

Exocytosis of packaged vesicle
b) Give a detailed account of thyroid hormone action and its recycling.
c) Discuss the following (any two) (2.5+ 2.5=5)

i) G- protein coupled receptor

Two kinds: "heterotrimeric G proteins" and "small G proteins. A model for their activity

- Binding of hormone, etc., to receptor protein in the membrane triggers dissociation of GDP and binding of GTP to a-subunit of G protein
- G\(_a\)-GTP complex dissociates from G\(_{bg}\) and migrates to effector sites, activating or inhibiting
- But it is now clear that G\(_{bg}\) also functions as a signaling device
ii) Guanylate cyclase

3. Guanylate cyclase (also known as guanylyl cyclase, guanylyl cyclase or GC) is a lyase enzyme. Guanylate cyclase is part of the G protein (does not use the G protein cascade in vertebrates) signaling cascade that is activated by low intracellular calcium levels and inhibited by high intracellular calcium levels. In response to calcium levels, guanylyl cyclase synthesizes cGMP from GTP. cGMP keeps cGMP-gated channels open, allowing for the entry of calcium into the cell. Like cAMP, cGMP is an important second messenger that internalizes the message carried by intercellular messengers such as peptide hormones and NO, and can also function as an autocrine signal. Depending on cell type, it can drive adaptive/developmental changes requiring protein synthesis. In smooth muscle, cGMP is the signal for relaxation, and is coupled to many homeostatic mechanisms including regulation of vascular and airway tone, insulin secretion, and peristalsis. Once formed, cGMP can be degraded by phosphodiesterases, which themselves are under different forms of regulation, depending on the tissue.

d) Describe the protein kinase C pathway with special reference to trigger of this pathway. 5

i. **Protein kinase C** also known as PKC is a family of protein kinase enzymes that are involved in controlling the function of other proteins through the phosphorylation of hydroxyl groups of serine and threonine amino acid residues on these proteins. PKC enzymes in turn are activated by signals such as increases in the concentration of diacylglycerol (DAG) or calcium ions (Ca\(^{2+}\)). Hence PKC enzymes play important roles in several signal transduction cascades. The PKC family consists of fifteen isoforms in humans. They are divided into three subfamilies, based on their second messenger requirements: conventional (or classical), novel, and atypical. Conventional (c)PKCs contain the isoforms α, β\(_1\), β\(_2\), and γ. These require Ca\(^{2+}\), DAG, and a phospholipid such as phosphatidylycerine for...
activation. Novel (n)PKCs include the \( \delta, \varepsilon, \eta, \) and \( \theta \) isoforms, and require DAG, but do not require \( \text{Ca}^{2+} \) for activation. Thus, conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. On the other hand, atypical (a)PKCs (including protein kinase \( \mu\zeta \) and \( \iota/\lambda \) isoforms) require neither \( \text{Ca}^{2+} \) nor diacylglycerol for activation. The term "protein kinase C" usually refers to the entire family of isoforms.

**Structure:** The structure of all PKCs consists of a regulatory domain and a catalytic domain tethered together by a hinge region. The catalytic region is highly conserved among the different isoforms, as well as, to a lesser degree, among the catalytic region of other serine/threonine kinase. The second messenger requirement differences in the isoforms are a result of the regulatory region, which are similar within the classes, but differ among them. Most of the crystal structure of the catalytic region of PKC has not been determined, except for PKC theta and iota. Due to its similarity to other kinases whose crystal structure have been determined, the structure can be strongly predicted.
e) Explain the followings

i. Hormone receptor pathophysiology

Hormones interact with their receptors to trigger intracellular cascades that ultimately result in diverse biological functions. These receptors that mediate hormone action are located either intracellularly or on the cell surface. Peptide hormone binds to cell surface receptors, causing release of second messenger molecules and activation of various intracellular signal transduction pathways which ultimately bring about their action. On the other hand, steroid hormones, iodothyronines, and calcitriol act on either cytoplasmic or nuclear receptors to produce changes in gene transcription and production of various proteins which subserve the cellular functions of these hormones. A classification of hormones based on the location of receptors and the second messenger pathway involved in signal transduction is presented in table I.

<table>
<thead>
<tr>
<th>I Hormones that bind to intracellular receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
</tr>
<tr>
<td>Oestrogens</td>
</tr>
<tr>
<td>Progestins</td>
</tr>
</tbody>
</table>

Retinoic acid | Calcitriol
α<sub>2</sub> adrenergic catecholamines | FSH, LH, PTH
β<sub>2</sub> adrenergic catecholamines | TSH
Calcitonin | Somatostatin
ACTH | Glucagon

| B. Cyclic GMP as second messenger
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Atriopeptides</td>
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<tr>
<td>Nitric oxide</td>
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<table>
<thead>
<tr>
<th>C. Calcium or phosphatidylinositides (or both) as second messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH</td>
</tr>
<tr>
<td>Angiotensin II</td>
</tr>
<tr>
<td>GnRH</td>
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</tbody>
</table>

<table>
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<tr>
<th>D. Kinase/phosphatase cascade as second messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
</tr>
<tr>
<td>Growth hormone</td>
</tr>
<tr>
<td>Epidermal growth factor</td>
</tr>
<tr>
<td>Insulin like growth factors I and II</td>
</tr>
<tr>
<td>Fibroblast growth factor</td>
</tr>
</tbody>
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The receptor concentration and function are maintained at optimal levels so as to facilitate appropriate target organ function. Receptor hyperfunction may result in target organ overstimulation producing clinical syndromes of hormone excess, while receptor hypofunction
may present with clinical features of hormone deficiency. The clinically important receptor diseases affecting the various hormone systems are described as follows:

**Thyroid receptor defects**

The TSH receptor bears structural homology with the adrenegic receptors and is linked to the G proteins for subsequent signal transduction. Thyroid disorders could result from disturbances in the G protein system or in the receptor function.

**Disorders affecting the G protein system**

Activating mutation of the proteins: Mutations in the $G_s$ protein α subunit can render the cells constitutively active, resulting in excessive production of cAMP and the subsequent events intracellularly. This mutant protein has been named as the $gsp$ oncogene. This has been found in patients with McCune Albright syndrome, a hereditary disorder characterised by autonomous hyperfunctioning of multiple endocrine tissues (including the thyroid), bony lesions (fibrous dysplasia), and irregularly shaped hyperpigmented skin lesions.

**TSH receptor mutations**

TSH-R mutations associated with hyper-thyroidism (gain in function): Mutations in the TSH-R gene have been found, which result in the unliganded TSH-R maintaining a conformation associated with the ligand bound state. This pseudo-activation of the TSH-R, in turn, leads to the ongoing stimulation of the G-protein signaling pathways by activation of the $G_s$ and $G_{q/11}$ proteins resulting in persistent elevations in intracellular cAMP, as well as activation of the phospholipase C pathway.

**Growth hormone receptor defect**

Genetic defects in the growth hormone receptor/IGF-1 receptor can lead to growth hormone insensitivity or Laron’s syndrome with clinical features of severe growth hormone deficiency, but markedly elevated levels of growth hormone (GH) and reduced levels of IGF-1. This disorder is caused by a number of molecular defects in the GH-R gene, particularly affecting the extracellular domain of the receptor, thereby reducing or abolishing the ability of GH to bind to the receptor. This disorder in many of the patients has an autosomal recessive mode of inheritance.

**Glucocorticoid receptor defect**

Glucocorticoid resistance is caused by an inherited mutation of the glucocorticoid receptor. Mutations occur in the glucocorticoid receptor ligand binding domain and at a splice site. Glucocorticoid resistance is a hypertensive disorder accompanied by hypokalaemia with suppressed renin and aldosterone. It is characterised by high levels of plasma cortisol and a paucity of stigmata of Cushing’s syndrome. An excess of adrenal androgens also occurs and in women it manifests with hirsutism and in children with precocious pseudopuberty.
ii. **Xenoestrogen**

**Xenoestrogens** are a type of xenohormone that imitates estrogen. They can be either synthetic or natural chemical compounds. Synthetic xenoestrogens are widely used industrial compounds, such as PCBs, BPA and phthalates, which have estrogenic effects on a living organism even though they differ chemically from the estrogenic substances produced internally by the endocrine system of any organism. Natural xenoestrogens include phytoestrogens which are plant-derived xenoestrogens. Because the primary route of exposure to these compounds is by consumption of phytoestrogenic plants, they are sometimes called "dietary estrogens". Mycoestrogens, estrogenic substances from fungi, are another type of xenoestrogen that are also considered mycotoxins.

Xenoestrogens are clinically significant because they can mimic the effects of endogenous estrogen and thus have been implicated in precocious puberty and other disorders of the reproductive system. Xenoestrogens include pharmacological estrogens (estrogenic action is an intended effect, as in the drug ethinyl estradiol used in contraceptive pill), but other chemicals may also have estrogenic effects.

**Mechanism:**

The onset of puberty is characterized by increased levels of hypothalamic gonadotropin releasing hormone (GnRH). GnRH triggers the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland, which in turn causes the ovaries to respond and secrete estradiol. Increases in gonadal estrogen promote breast development, female fat distribution and skeletal growth. Adrenal androgen and gonadal androgen result in pubic and axillary hair. Peripheral precocious puberty caused by exogenous estrogens is evaluated by assessing decreased levels of gonadotrophins.

Hormones or substances with hormone disrupting capability may interfere with pubertal development by actions at different levels – hypothalamic-pituitary axis, gonads, peripheral target organs such as the breast, hair follicles and genitals. Exogenous man made chemicals that mimic estrogen can alter the functions of the endocrine system and cause various health defects by interfering with synthesis, metabolism, binding or cellular responses of natural estrogens.

Although the physiology of the reproductive system is complex, the action of environmental exogenous estrogens is hypothesized to occur by two possible mechanisms. Xenoestrogens may temporarily or permanently alter the feedback loops in the brain, pituitary, gonads, and thyroid by mimicking the effects of estrogen and triggering their specific receptors or they may bind to hormone receptors and block the action of natural hormones. Thus it is plausible that environmental estrogens can accelerate sexual development if present in a sufficient concentration or with chronic exposure. The similarity in the structure of exogenous estrogens and the estrogens has changed the hormone balance within the body and resulted in various reproductive problems in females. The overall mechanism of action is binding of the exogenous compounds that mimic estrogen to the estrogen binding receptors and cause the determined action in the target organs.

Another potential effect of xenoestrogens is on oncogenes, specifically in relation to breast cancer. Some scientists doubt that xenoestrogens have any significant biological effect, in the concentrations found in the environment. However, there is substantial evidence in a variety of recent studies to indicate that xenoestrogens can increase breast cancer growth in tissue culture.
It has been suggested that very low levels of a xenoestrogen, Bisphenol A, could affect fetal neural signalling more than higher levels, indicating that classical models where dose equals response may not be applicable in susceptible tissue. As this study involved intra-cerebellar injections, its relevance to environmental exposures is unclear, as is the role of an estrogenic effect compared to some other toxic effect of bisphenol A.

Common environmental estrogen

Atrazine, BPA, (Bisphenol A), DDT DDT (Dichlorodiphenyltrichloroethane), Dioxin, a group of highly toxic chemicals, Endosulfan an insecticide, PBB (Polybrominated biphenyls), PCBs, Phthalates, Zeranol

e) Give the structural and functional aspects of MAP kinase pathway.

**MAP Kinase Pathways can be mediated by members of the Ras superfamily**
f) Discuss about - Hormone analogous, Synergism and antagonism  

Synthetic hormones which has different structure but similal physiological effect. e. g many steroid hormone, Xenosterogen.

The process of hormone acting on the same pathway of signal transduction is synergism.

Ref of Membrane and Steroid receptor Mechaism of Action has to be discussed commonly.

Inhibitory action of any hormone for a particular one is called and antagonistic behavior and the phenomena is antagonism.