AV-8190

Model answer

M.Sc. Semester-III

Paper LZT 303(A): Neuroendocrinology and Non-classical Hormones

Q 1

Answer

(i) d	(ii) a	(iii) d	(iv) b	(v) c
(vi) d	(vii) a	(viii) d	(ix) d	(x) b

Q 2

Answer

The **hypothalamic–pituitary–adrenal axis** (**HPA** or **HTPA axis)** is a set of interactions among three endocrine glands: the hypothalamus, the pituitary gland and the adrenal glands. The interactions among these organs constitute the **HPA axis**, a major part of the neuroendocrine system that controls reactions to stress and regulates many body processes, including digestion, the immune system, sexuality, and energy storage and expenditure. It is the common mechanism for interactions among glands, hormones, and parts of the midbrain that mediate the general adaptation syndrome.

The key components of the HPA axis are:

- The paraventricular nucleus of the hypothalamus, which contains neuroendocrine neurons that synthesize and secrete vasopressin and corticotropin-releasing hormone (CRH). These two peptides regulate:
- The anterior lobe of the pituitary gland. In particular, CRH and vasopressin stimulate the secretion of adrenocorticotropic hormone (ACTH), once known as **corticotropin**. ACTH in turn acts on:
- the adrenal cortex, which produces glucocorticoid hormones (mainly cortisol in humans) in response to stimulation by ACTH. Glucocorticoids in turn act back on the hypothalamus and pituitary (to suppress CRH and ACTH production) in a negative feedback cycle.

CRH and vasopressin are released from neurosecretory nerve terminals at the median eminence. CRH is transported to the anterior pituitary through the portal blood vessel system of the hypophyseal stalk and vasopressin is transported by axonal transport to the posterior pituitary.

There, CRH and vasopressin act synergistically to stimulate the secretion of stored ACTH from corticotrope cells. ACTH is transported by the blood to the adrenal cortex of the adrenal gland, where it rapidly stimulates biosynthesis of corticosteroids such as **cortisol** from cholesterol. Cortisol is a major stress hormone and has effects on many tissues in the body, including the brain. In the brain, cortisol acts on two types of receptor – mineralocorticoid receptors and glucocorticoid receptors, and these are expressed by many different types of neurons. One important target of glucocorticoids is the hypothalamus, which is a major controlling centre of the HPA axis.

Vasopressin can be thought of as "water conservation hormone" and is also known as "antidiuretic hormone." It is released when the body is dehydrated and has potent water-conserving effects on the kidney. It is also a potent vasoconstrictor.

Important to the function of the HPA axis are some of the feedback loops:

- Cortisol produced in the adrenal cortex will negatively feedback to inhibit both the hypothalamus and the pituitary gland. This reduces the secretion of CRH and vasopressin, and also directly reduces the cleavage of proopiomelanocortin (POMC) into ACTH and β-endorphins.
- Epinephrine and norepinephrine are produced by the adrenal medulla through sympathetic stimulation and the local effects of cortisol (upregulation enzymes to make E/NE). E/NE will positively feedback to the pituitary and increase the breakdown of POMCs into ACTH and β-endorphins.

Function

Release of CRH from the hypothalamus is influenced by stress, physical activity, illness, by blood levels of cortisol and by the sleep/wake cycle (circadian rhythm). In healthy individuals, cortisol rises rapidly after wakening, reaching a peak within 30–45 minutes. It then gradually falls over the day, rising again in late afternoon. Cortisol levels then fall in late evening, reaching a trough during the middle of the night. This corresponds to the rest-activity cycle of the organism. An abnormally flattened circadian cortisol cycle has been linked with chronic fatigue syndrome, insomnia and burnout.

The HPA axis has a central role in regulating many homeostatic systems in the body, including the metabolic system, cardiovascular system, immune system, reproductive system and central

nervous system. The HPA axis integrates physical and psychosocial influences in order to allow an organism to adapt effectively to its environment, use resources, and optimize survival.

Anatomical connections between brain areas such as the amygdala, hippocampus, prefrontal cortex and hypothalamus facilitate activation of the HPA axis. Sensory information arriving at the lateral aspect of the amygdala is processed and conveyed to the central nucleus, which projects to several parts of the brain involved in responses to fear. At the hypothalamus, fear-signaling impulses activate both the sympathetic nervous system and the modulating systems of the HPA axis.

Increased production of cortisol during stress results in an increased availability of glucose in order to facilitate fighting or fleeing. As well as directly increasing glucose availability, cortisol also suppresses the highly demanding metabolic processes of the immune system, resulting in further availability of glucose.

Glucocorticoids have many important functions, including modulation of stress reactions, but in excess they can be damaging. Atrophy of the hippocampus in humans and animals exposed to severe stress is believed to be caused by prolonged exposure to high concentrations of glucocorticoids. Deficiencies of the hippocampus may reduce the memory resources available to help a body formulate appropriate reactions to stress.

Q 3

Answer

Growth hormone releasing hormone

Growth-hormone-releasing hormone (GHRH), also known as growth-hormone-releasing factor (GRF, GHRF) is a releasing hormone for growth hormone. It is a 44-amino acid peptide hormone produced in the arcuate nucleus of the hypothalamus.

GHRH first appears in the human hypothalamus between 18 and 29 weeks of gestation, which corresponds to the start of production of growth hormone and other somatotropes in fetuses.

Origin

GHRH is released from neurosecretory nerve terminals of these arcuate neurons, and is carried by the hypothalamo-hypophyseal portal system to the anterior pituitary gland, where

it stimulates growth hormone (GH) secretion by stimulating the growth hormone-releasing hormone receptor. GHRH is released in a pulsatile manner, stimulating similar pulsatile release of GH. In addition, GHRH also promotes slow-wave sleep directly. Growth hormone is required for normal postnatal growth, bone growth, regulatory effects on protein, carbohydrate, and lipid metabolism.

Effect

GHRH stimulates GH production and release by binding to the GHRH Receptor (GHRHR) on cells in the anterior pituitary.

Receptor

The GHRHR is a member of the secretin family of G protein-coupled receptors. This protein is transmembranous with seven folds, and its molecular weight is approximately 44 kD.

Signal transduction

GHRH binding to GHRHR results in increased GH production mainly by the cAMP-dependent pathway, but also by the phospholipase C pathway (IP_3/DAG pathway), and other minor pathways.

The cAMP-dependent pathway is initiated by the binding of GHRH to its receptor, causing receptor conformation that activates G_s alpha subunit of the closely associated G-Protein complex on the intracellular side. This results in stimulation of membrane-bound adenylyl cyclase and increased intracellular cyclic adenosine monophosphate (cAMP). cAMP binds to and activates the regulatory subunits of protein kinase A (PKA), allowing the free catalytic subunits to translocate to the nucleus and phosphorylate the transcription factor cAMP response element-binding protein (CREB). Phosphorylated CREB, together with its coactivators, p300 and CREB-binding protein (CBP) enhances the transcription of GH by binding to CREs cAMP-response elements in the promoter region of the GH gene. It also increases transcription of the GHRHR gene, providing positive feedback.

In the phospholipase C pathway, GHRH stimulates phospholipase C (PLC) through the βγ-complex of heterotrimeric G-proteins. PLC activation produces both diacylglycerol (DAG) and inositol triphosphate (IP_3), the latter leading to release of intracellular Ca^{2+} from the endoplasmic reticulum, increasing cytosolic Ca^{2+} concentration, resulting in vesicle fusionand release of secretory vesicles containing premade growth hormone.

Some Ca^{2+} influx is also a direct action of cAMP, which is distinct from the usual *cAMP-dependent pathway* of activating *protein kinase A*.

Activation of GHRHRs by GHRH also conveys opening of Na+ channels by phosphatidylinositol 4,5-bisphosphate, causing cell depolarization. The resultant change in the intracellular voltage opens a voltage-dependent calcium channel, resulting in vesicle fusion and release of GH.

(i) Somatostatin

Somatostatin (also known as growth hormone-inhibiting hormone (GHIH) or somatotropin release-inhibiting factor (SRIF)) or somatotropin release-inhibiting hormone is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Somatostatin regulates insulin and glucagon.

Somatostatin has two active forms produced by alternative cleavage of a single preproprotein: one of 14 amino acids, the other of 28 amino acids.

In all vertebrates, there exist six different somatostatin genes that have been named SS1, SS2, SS3, SS4, SS5, and SS6. The six different genes along with the five different somatostatin receptors allows somatostatin to possess a large range of functions. Humans have only one somatostatin gene, SST.

Production

Digestive system

Somatostatin is secreted in several locations in the digestive system:

- stomach
- intestine
- delta cells of the pancreas

Somatostatin will travel through the portal blood system, to the heart, then to systemic circulation, where it will exert its digestive system effects. In the stomach, somatostatin acts on the acid-producing parietal cells via G-coupled receptor to reduce secretion. Somatostatin also indirectly decreases stomach acid production by preventing the release of other hormones, including gastrin, secretin and histamine which effectively slows down the digestive process.

Brain

Somatostatin is produced by neuroendocrine neurons of the ventro medial nucleus of the hypothalamus. These neurons project to the median eminence, where somatostatin is released from neurosecretory nerve endings into the hypothalamo-hypophysial system through neuron axons. Somatostatin is then carried to the anterior pituitary gland, where it inhibits the secretion of growth hormone from somatotrope cells. The somatostatin neurons in the periventricular nucleus mediate negative feedback effects of growth hormone on its own release; the somatostatin neurons respond to high circulating concentrations of growth hormone and somatomedins by increasing the release of somatostatin, so reducing the rate of secretion of growth hormone.

Somatostatin is also produced by several other populations that project centrally, i.e., to other areas of the brain, and somatostatin receptors are expressed at many different sites in the brain. In particular, there are populations of somatostatin neurons in the arcuate nucleus, the hippocampus, and the brainstem nucleus of the solitary tract

Somatostatin is classified as an inhibitory hormone, whose actions are spread to different parts of the body:

Anterior pituitary

In the anterior pituitary gland, the effects of somatostatin are:

- Inhibit the release of growth hormone (GH) (thus opposing the effects of Growth Hormone-Releasing Hormone(GHRH))
- Inhibit the release of thyroid-stimulating hormone (TSH)
- It is induced by low pH.
- Inhibit adenylyl cyclase in parietal cells.
- Inhibits the release of prolactin (PRL)

Gastrointestinal system

- Somatostatin is homologous with cortistatin and suppresses the release of gastrointestinal hormones
    - Gastrin
    - Cholecystokinin (CCK)
    - Secretin

- Motilin
- Vasoactive intestinal peptide (VIP)
- Gastric inhibitory polypeptide (GIP)
- Enteroglucagon

- Decrease rate of gastric emptying, and reduces smooth muscle contractions and blood flow within the intestine
- Suppresses the release of pancreatic hormones
  - Inhibits insulin release when somatostatin is released from delta cells of pancreas
  - Inhibits the release of glucagon
- Suppresses the exocrine secretory action of pancreas.

Q 4

Answer

Physiological roles of Melatonin

Melatonin secretion is related to the duration of darkness. The main function of melatonin is to mediate dark signals, with possible implications in the control of circadian rhythmicity and seasonality. The melatonin message, which is generated at night, is differently read in nocturnal animals and humans. In that sense, melatonin does not appear as the universal hormone of sleep. The role of melatonin for the seasonal changes in physiology and behaviour of arious photoperiodic species has been extensively documented. For a long time, humans were claimed to be poorly sensitive to photoperiod variations, as no difference between the summer and winter melatonin duration was found in temperate zones. Studies conducted under appropriate natural or controlled laboratory conditions show that humans also exhibit changes in the daily profile of melatonin. It is proposed that the circadian pacemaker consists of two component oscillators. One is entrained to dusk and controls the onset of melatonin secretion, the other is entrained to dawn and controls the offset. The dusk and dawn entrained components of the circadian pacemaker could be considered to control evening and morning transitions in melatonin secretion and to adjust the timing of these transitions in seasonal changes in day length.

Melatonin, the endogenous synchroniser

The time of melatonin secretion adjusts to the light/dark cycle. A general opinion is that melatonin, by providing the organism with the night information, could be an endogenous

synchronizer able to stabilize circadian rhythms, to reinforce them and to maintain their mutual phase-relationship.

Antioxidant activity

Melatonin is a potent free radical scavenger. Melatonin directly scavenges the highly toxic hydroxyl radical and other oxygen centered radicals. Also, melatonin displays antioxidative properties: it increases the levels of several antioxidative enzymes including superoxide dismutase, glutathione peroxidase and glutathione reductase. On the other hand, melatonin inhibits the pro-oxidative enzyme nitric oxide synthase. Since considerable experimental evidence supports the idea that oxidative stress is a significant component of specific brain diseases, the ability of melatonin to protect against neurodegeneration has been tested in a multitude of models.

Immunity

Currently accumulated evidence shows that the pineal is able to play an important role in modulating the immune response. Melatonin can interact with specific membrane binding sites in cells from lymphoid organs. In addition, interactions between the pineal gland and the immune system are bidirectional since interleukins and cytokines affect melatonin synthesis and release.

Q 5

Answer

Anti mullerian hormone and function:-

Anti-Mullerian hormone also known as AMH is a protein that, in humans, is encoded by the *AMH* gene. It inhibits the development of the Mullerian ducts (paramesonephric ducts) in the male embryo. It has also been called Mullerian inhibiting factor (MIF), Mullerian-inhibiting hormone (MIH), Mullerian-inhibiting substance (MIS), and Anti-paramesonephric hormone (APH). It is named after Johannes Peter Muller.

AMH works by interacting with specific receptors on the surfaces of the cells of target tissues. The best-known and most specific effect, mediated through the AMH type II receptors, includes programmed cell death (apoptosis) of the target tissue (the fetal Müllerian ducts).

Although the AMH receptor is expressed in both male and female fetuses, AMH expression has been isolated to male sertoli cells. Expression of AMH is activated by SOX9 in the male sertoli cells and causes the irreversible regression of the Müllerian ducts. Because AMH expression is critical to sex differentiation at a specific time during fetal development, it appears to be tightly

regulated by SF1, GATA factors, DAX1 and FSH. Mutations in both the AMH gene and the type II AMH receptor have been shown to cause the persistence of Müllerian derivatives in males that are otherwise normally virilized.

AMH expression also occurs in ovarian granulosa cells of females postpartum, and serves as a molecular biomarker for relative size of the ovarian reserve. In humans, the number of cells in the follicular reserve can be used to predict timing of menopause. In bovine, AMH can be used for selection of females in multi-ovulatory embryo transfer programs by predicting the number of antral follicles developed to ovulation

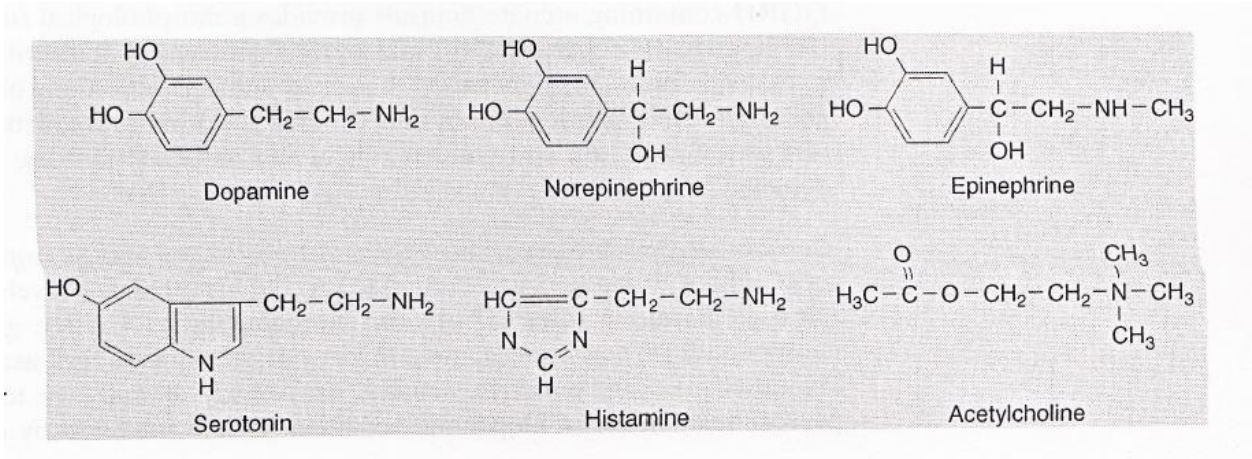
AMH is expressed by granulosa cells of the ovary during the reproductive years, and limits the formation of primary follicles by inhibiting excessive follicular recruitment by FSH.

AMH production by the Sertoli cells of the testes remains high throughout childhood in males but declines to low levels during puberty and adult life. AMH has been shown to regulate production of sex hormones.

Q 6

Answer

Pituitary responses are regulated by hypophysiotropic hormones. Brain is mainly composed mainly of neurons and supporting elements, other neurons within the brain are expected to regulate the hypophysiotropin-secreting neurons. These other neurons, in turn, are linked to yet other neuronal inputs such as sensory neurons that are receptive to endogenous (intrinsic) and exogenous (extrinsic) cues. Intrinsic and extrinsic stimuli received through sensory neurons are conducted through neuronal routes to the brain where this information may be inhibitory of stimulatory to hypophysiotropic hormone secretion.



The monoamine neurotransmitters

Conduction of sensory information is via neuronal elements, and each nerve must release a neurotransmitter to effect synaptic transmission. These neurohormones include the monoamine neurotransmitters and the amino acid neurotransmitter. There are well-defined aminergic (monoamine) pathways within the brain that are composed of serotonergic, dopaminergic, noradrenergic, and even epinephrine-containing neurons.

Specific neurotransmitters regulate hypophysiotropin secretions

Control of CRH secretion

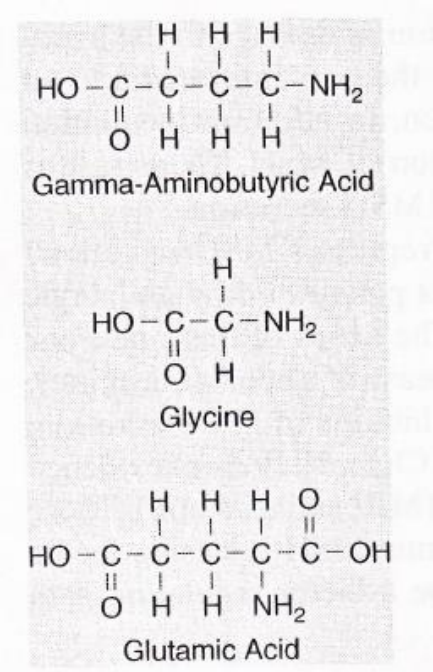
- A number of neurotransmitter are involved.
- Stress is a potent stimulus to ACTH secretion.
- One or more cholinergic pathways are involved.
- Stimulation of CNS cholinergic structures provokes ACTH release.
- Catecholamines induce release of both CRH and AVP.

Control of PIF secretion

- Suckling is normal stimulus to PRL secretion.
- This involves the inhibition of dopaminergic neurons.
- A number of neurotransmitters are involved in control of PRL secretion.
- Nocturnal rise in PRL secretion involves activation of serotonergic neurons.
- GABA may also control PRL secretion.

Control of growth hormone secretion

- A variety of stimuli elevate GH secretion, through inhibition of somatostatin secretion or by an enhancement of GHRH secretion.
- Finding of SST receptors on GHRH-containing arcuate neurons signifies the concept of direct “cross-talk” between SST and GHRH neuronal system.
- This interaction may be a vital component in generation and maintenance of the ultradian rhythm of GH secretion.



The amino acid neurotransmitters

Control of GnRH secretion

- Several transmitters and neuropeptides participates in regulation of gonadotropin secretion.
- At the level of hypothalamus, control of GnRH involves norepinephrine, GABA, glutamate, angiotensin II, neuropeptide T, neurotensin, and 5-hydroxytryptamine, as well as interleukins 1 and 2.
- Dopaminergic neurons are clearly stimulatory to GnRH release.
- Dopamine secretion itself is inhibited by enkephalinergic neurons.

Control of TRH secretion

- Apparently noradrenergic neurons stimulate TSH secretion by a stimulatory action on TRH-secreting neurons.
- Glucocorticoids excess inhibits thyroid function at a suprapituitary level.
- A complex array of othe rfactors influence TRH production.

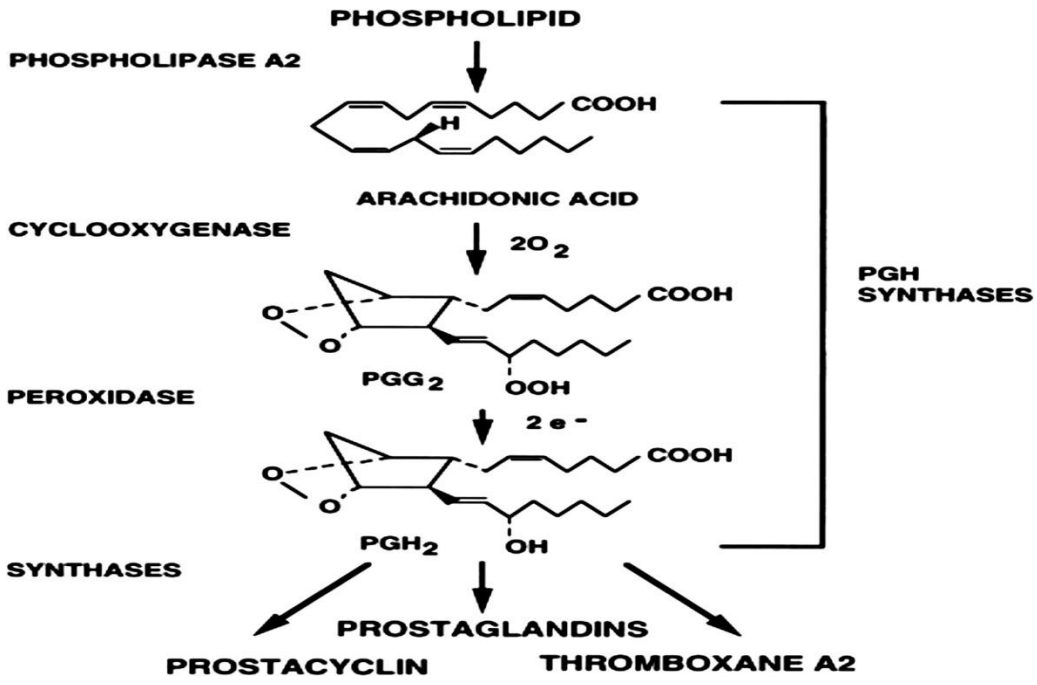
Q 7

Answer

The **prostaglandins** are a group of physiologically active lipid compounds having diverse hormone-like effects in animals. Prostaglandins and related molecules are called eicosanoids as a class. The term 12icosanoid is derived from "eicosa" meaning "twenty", referring to the 20 carbons in most of the molecules. The eicosanoids are used as 12icosanoid molecules. They generally act locally, either affecting cell that makes them or nearby cells; in most cases, eicosanoids are not systemic hormones, because of their short half-lives.

Prostaglandin biosynthesis has two control points. Phospholipase A2 The starting material for prostaglandin biosynthesis is a fatty acid. The fatty acid used is nearly always derived from the 2-position of a membrane phospholipid (usually phosphatidylinositol).

The second control point is the enzyme responsible for converting the fatty acid to the first molecule in the relevant pathway. Two enzymes are primarily involved in 12icosanoid biosynthesis. Prostaglandin synthase and 5-lipoxygenase. Prostaglandin synthase is a complex enzyme that catalyzes the first two steps in the prostaglandin synthesis pathway. It is often called cyclooxygenase (referring to the first of the two reactions it mediates); cyclooxygenase.



Prostaglandin action is incompletely understood. Known actions include:

- ✓ Induction of inflammation
- ✓ Mediation of pain signals
- ✓ Induction of fever
- ✓ Smooth muscle contraction (including uterus) – (especially PGF2α)
- ✓ Smooth muscle relaxation – especially PGE series
- ✓ Protection of stomach lining
- ✓ Stimulation of platelet aggregation (thromboxanes)

Q 8

Answer

HEMATOPOIETIC GROWTH FACTORS

- ✓ They are heterogeneous group of cytokines that stimulate the progenitor cells and induce proliferation and maturation
- ✓ They are glycoproteins synthesized by variety of cells in marrow.
- ✓ They bind to specific receptors on the surface of various cells of the hematopoietic system

Characteristic and properties

i. Naturally occurring hormones.
ii. Low molecular weight glycoprotiens.
iii. Variable degrees of species specificity.
iv. Available in purified form by recombinant DNA technology.
v. Responsible for stimulation and release of other growth factors and cytokines.

1.Erythropoitein

- ✓ Erythropoitein also called hematopoietein, it is produced by interstitial fibroblasts in the kidney in close association with peritubular capillary and proximal convoluted tubule in response to hypoxemia
- ✓ Present in minute amounts in urine
- ✓ Liver secretes 10% of endogenous erythropoietin.
- ✓ Responsible for low level erythroid activity.
- ✓ Half life of 6-9 hrs. in anemic patient

2. Thrombopoietin

- ✓ It is a glycoprotein hormone produced mainly by liver and kidney that regulates the production of platelets in bone marrow. It is also known as megakaryocyte growth and development factor.
- ✓ It stimulates the production and differentiation of Megakaryocytes

3.GM-CSF:

- ✓ Produced by fibroblasts, stromal cells,T-lymphocytes and endothelial cells.
- ✓ Stimulate progenitors for granulocytes, monocytes and erythrocytes

4. G-CSF:

- ✓ LMW glycoprotein
- ✓ Stimulates proliferation and maturation of granulocyte precursors.

- ✓ Produced by stromal cells, monocytes, macrophages, and endothelial cells.

5.M-CSF

- ✓ Secreted by stromal cells, macrophages and fibroblasts.
- ✓ Heavily glycosylated glycoprotein
- ✓ Potent stimulator of macrophage function and activation as it increases the expression of MHC.II antigen on macrophages.