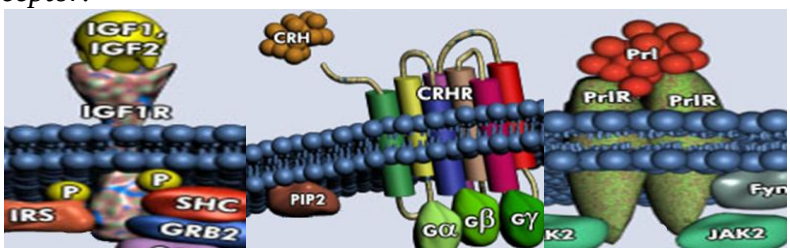
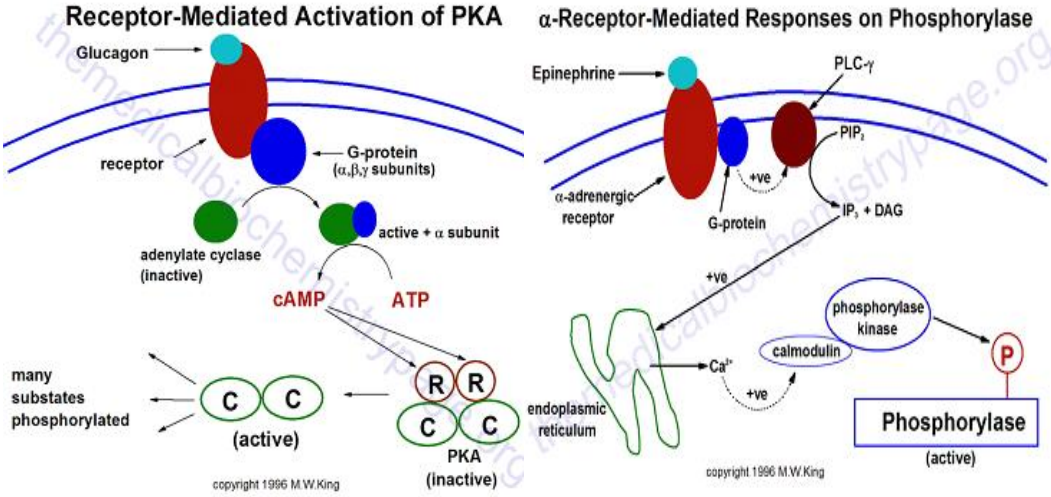
Unit IV – Problem 6 – Biochemistry: Hypothalamo-Pituitary Hormones

- **Pituitary gland is located under the hypothalamus and is divided into two lobes:**
  - **Anterior (adenohypohpysis).**
  - **Posterior (neurohypophysis).**
- Hypothalamus secretes releasing factors which stimulate the release of corresponding tropic hormones from anterior pituitary gland. These tropic hormones –in turn- will exert their effects on their target endocrine tissues.
- **Steroid hormone receptors:**
  - Steroid are hydrophobic molecules which diffuse across cell membranes and bind to their cytosolic receptors to form steroid-receptor complex. This complex will enter the nucleus and bind to hormone-response elements (HRE) DNA regions thus altering gene expression.
- **Peptide hormone receptors (these are located in the plasma membrane):**
  - **Receptor structure:**
    - ✓ Single chain with extracellular, intracellular and transmembrane domains**.** *Example: IGF-receptor.*
    - ✓ Single chain with multiple intracellular, extracellular and transmembrane domains. *Example: CRH*
    - ✓ Other receptors consisting of multiple chains. *Examples: insulin receptor and T-cell receptor.*



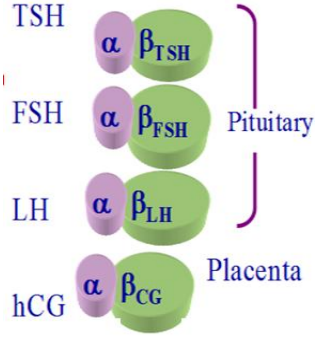
- **Second messenger system:**
  - **Principle second messengers are:**
    - ✓ **cAMP**: activation of G-protein couples receptors results in activation of adenylate cyclase (↑cAMP) which results in cAMP-dependent protein kinase (leading to phosphorylation).
    - ✓ **Ca^{2+}/ inositol triphosphate/ diacylglycerol (DAG):** hydrolysis of PIP2 yielding two messengers:
      - ❖ Inositol triphosphate (IP_3): resulting in the release of calcium stores from endoplasmic reticulum which will activate Ca^{2+}-dependent enzymes.
      - ❖ Diacylglycerol (DAG): activating protein kinase C (PKC) which opens voltage-gated Ca^{2+}-channels thus reinforcing (IP_3) effect.



- **Hypothalamic hormones:**

Hormone	Function
Gonadotropin-Releasing Hormone (GnRH)	Stimulating adenohypophysis to produce LH & FSH
Corticotropin-Releasing Hormone (CRH)	Stimulating adenohypophysis to secrete (ACTH) which –in turn- stimulate the release of corticosteroids from adrenal cortex
Growth Hormone Releasing Hormone (GHRH)	Stimulating growth hormone (somatotropin) secretion from adenohypophysis to promote growth
Growth Hormone Inhibiting Hormone (GHIH)	Known as somatostatin and it inhibits GH and TSH secretion from adenohypohpysis
Thyrotropin-Releasing Hormone (TRH)	Stimulating (TSH) secretion from adenohypohpysis which –in turn- enhances thyroid hormones production from thyroid gland
Prolactin Release-Inhibiting Hormone (dopamine)	-
Prolactin-Releasing Factor (PRF)	Stimulating prolactin release

- **Anterior pituitary hormones:**
  - **Categories of pituitary hormones:**
    - ✓ Growth hormone-prolactin group: growth hormone, prolactin and chorionic somatomammotropin are similar to each other.
    - ✓ Glycoprotein hormones: structural but not fanctional similarity. This group includes the following: TSH, FSH, LH and hCG.
    - ✓ Pro-opiomelanocortin peptide group: produced from a single gene of the anterior and intermediate pituitary lobes. This group includes the following: ACTH, lipoprotein and MSH
- **Growth hormone (GH):**
  - It is the most abundant hormone in pituitary gland.
  - Secretion is pulsatile with a half-life of 25 minutes (in lean adults).
  - 40% of (GH) is bound to GH-binding protein (GHBP).
  - **Mechanism of action**: (GH) binds to its receptor and results in activation of Jak-2.
  - **Abnormalities of (GH) production:**
    - ✓ Impaired (GH) secretion in children results in dwarfism.
    - ✓ Excessive (GH) production results in gigantism (in children) or acromegaly (in adults). Notice that acromegaly promotes insulin resistance which results in cardiovascular complications.
  - **Insulin-Like Growth Factors (IGFs):**
    - ✓ Responsible for growth-promoting effects of (GH).
    - ✓ IGF-2 is the primary growth factor needed for early development while IGF-1 expression is needed for achieving maximal growth.
- **Prolactin:**
  - Produced by ascidophils in anterior pituitary gland. Its synthesis is inhibited by dopamine.
  - **Receptors are present in**: mammary glands, liver, gonads, uterus, prostate, adrenals and kidney.
  - Prolactin release increases during pregnancy and lactation and is enhanced by estrogen and oxytocin.
- **Glycoprotein hormones:**
  - **Composed of two subunits**: α-subunit being similar in all of them while β-subunit is the one which is different.
  - LH, FSH and hCG bind to cells in ovaries and testes → stimulating the production of the steroid sex hormones (estrogen, testosterone and dehydrotestosterone).
  - TSH stimulates the thyroid gland to secrete T3 and T4.



- **Pro-opiomelanocortin (POMC):**
  - Expressed in anterior and intermediate pituitary lobes.
  - POMC is a pro-hormone which is processed to opioids, Melanocyte-Stimulating Hormone (MSH) and corticotrophin.
  - **POMC consists of three peptide groups:**
    - ✓ ACTH which can give rise to α-MSH (the only type which is important in humans) and corticotrophin-like intermediate lobe peptide (CLIP). α-MSH stimulates the production of melanin by binding to melanocrotin-1 receptor which is then transported and deposited in keratinocytes resulting in pigmentation.
    - ✓ β-lipotropin which can produce γ-LPH and β-MSH. It is present only in the pituitary gland and it promotes lipolysis and mobilization of fatty acids.
    - ✓ An N-terminal peptide that forms γ-MSH.
  - **POMC processing involves**: glycosylation, acetylation and extensive proteolytic cleavage at sites that contain basic protein sequences.
  - POMC and its related products occur in several tissues (brain, lung, placenta and GI tract).
- **Adrenocorticotropic hormone (ACTH):**
  - **Function**: stimulating the production of glucocorticoids (from zona fasciculata) and adrenal androgens (from zona reticularis) of adrenal cortex. Notice that it has an intrinsic melanocyte-stimulating activity.
  - **Cushing disease results from excessive secretion of ACTH**, characterized by hyperpigmentation and increased production of adrenal steroids.
  - **ACTH deficiency results in reduction of adrenal cortex** (especially in zona fasciculata and zona reticularis).
- **Posterior pituitary hormones:**
  - **What are they?**
    - ✓ Vasopressin, also known as antidiuretic hormone (ADH):
      - ❖ *Secretion is stimulated by*: increased plasma osmolarity.
      - ❖ *Function*: stimulating the absorption of pure water from collecting tubules of kidneys thus increasing blood pressure and producing concentrated urine.
    - ✓ Oxytocin:
      - ❖ *Synthesized from*: magnocellular neurons.
      - ❖ *Functions:*
        - ➢ Contraction of the uterus (parturition).
        - ➢ Ejection of milk.
        - ➢ Oxytocin is also increased in males during ejaculation.

    Note: both of these hormones are synthesized in neural cell bodies which are present in hypothalamus and then transported through axons to be stored in neurohypophysis.