A P T E R Basic Concepts of Endocrine Regulation 1 6 O B J E C T I V E S After studying this chapter, you should be able to: o Describe hormones and their contribution to whole body homeostatic mechanisms.Secretion rats may peak and ebb "trough" relative to circadian rhythms (day and nigh times) in response to meal timing, other periodically changed regulators which may range from millisecond to years – according to the age and development) ? The oscillator in the hypothalamus regulates the membrane potential of hypothalamic neurons and thus determine the pulsatile secretion of trophic factors into hypophysial blood supplies the pituitary gland hormones and hence the pulsatile manner of pituitary hormone secretion. ? These hormone pulses convey different information to target tissues on which they act compared to a steady state secretion rate. ? Factors influencing the circulating level of hormones: 1. Rate of secretion 2. 3. 4. 5. Nature of secretion (steady vs pulsatile) Rate of degradation and uptake Affinity of binding to receptor and receptors availability Affinity to carrier plasma proteins ? Hormone stability (resistance to degradation or loss) influence the half-life of a hormone and offer a therapeutic implications for hormone replacement therapy (by synthesizing more stable analogues): ? Keep in mind: Only the FREE hormone is biologically active in target tissue and the only can mediate the feedback regulation (since it is the only form able to access the extravascular compartment) ? Plasma carriers which ultimately modulate the level of free hormone in plasma. Their functions are below: 1. 2. 3. They serve as a reservoir of inactive hormone and thus provide a hormonal reserve. They prevent degradation or uptake of bound hormone and allow for smoothed hormonal level over time. They restrict the access of hormone to some sites. ? Adrenaline & most peptide are soluble in plasma and do not require a transport. ? Estradiol & testosterone bind to SBG ? Progesterone, cortisol and glucocorticoids bind to Transcortin. ? The SBP-hormone complex and the free hormone are in equilibrium in the plasma, and only the free hormone can diffuse across cell membranes SBP have 3 main functions: (1) They increase the solubility of lipid-based hormones in the blood; (2) They reduce the rate of hormone loss in the urine by preventing the hormones from being altered in the kidney (3) They provide a source of hormone in the bloodstream that can release free hormone as the equilibrium changes (reservoir). Additional way to regulate the availability of hormones is to regulate the expression and secretion of the carrier proteins themselves. This is a critical mechanism that regulates the bioavailability of thyroid hormones, for example. Finally, several hormones are destroyed by passage through the pulmonary circulation or the liver . This may markedly curtail the temporal window (peak and trough plasma level) within which a given hormone can act. ? Peptides and catecholamines (Hydrophilic hormones), exert their acute effects by binding to cell surface receptors (most are of the GPCR family). ? Steroids and thyroxine (Hydrophobic hormones), predominantly exert their actions via nuclear receptors. ? Two classes of nuclear receptors are important in endocrine physiology when a hormone bind them: 1. Those directly stimulate the transcription via induction of the binding of a transcriptional co- activator . 2. Those indirectly stimulate the transcription via dislodging of a transcriptional co-repressor and recruitment of a co-activator . The latter class of receptor allows for a wider dynamic range of regulation of the genes targeted by the hormone in question ? Feedback loops are either negative or positive. ? Positive feedback loop: involves the enhancement or continued stimulation of the original release mechanism/stimulus (this seen in parturition "delivery").Example: T4 bind nuclear genes on suppressor

regulatory sites of the TSH dictating gene in the pituitary gland ended with suppression of TSH synthesis.Since the regulatory regions of many peptide hormone genes contain binding sites for nuclear receptors, other hormones can control the synthesis of the peptide hormones ?Synthesis involved entry of cholesterol across the inner membrane of mitochondria by a specific carrier (StAR)– a first limiting step in the synthesis of the hormone precursor (pregnenolone).o Define how hormones are synthesized and secreted by cells of endocrine glands, including how peptide hormones are cleaved from longer precursors.o Explain the relevance of protein carriers in the blood for hydrophobic hormones, and the mechanisms that determine the level of free circulating hormones.It operates as a distributed network comprising glands and circulating messengers, often under the influence of the CNS, the autonomic nervous system, or both ?The hormone–receptor complex form dimer with a distinct ligand nuclear receptor that in turn bind DNA and cause gene transcription Control of synthesis: ?Amine and steroids: by regulating enzyme and substrates availability involved in the synthesis of the hormone.The endocrine system differs from other physiological systems in that it cannot be distinctly defined based on anatomical boundaries.Example of co–evolution: co–evolution of surface GPCR and tyrosine kinases for peptide and amine hormones. Steroid and T4 hormones have intracellular cytoplasmic receptors (they freely cross cell membrane).Thus multiple hormones my be derived from the same initial precursor (pre–pro–hormone).High glucose level increase the interaction of insulin– mRNA with specific RNA binding proteins.Peptide hormones are stored in secretory vesicles (granules) of secreting cells.A specific signal (neurotransmitter, hormone, peptide) activate the exocytosis of stored granules.Trophic hormones and cytokines bind their receptors on steroid secreting cells.Hormones grouped into families according to their structural similarities according to their similarities of the receptors they activate.These vesicles will contain the hormone and its inactive fragments and designed to export the hormone out of the cell ?These interactions increase stability and translation of insulin– mRNA and hence high level of insulin in blood after meal.o Understand the principles of feedback control for hormone release and its relevance for homeostasis.Hormones comprises of: steroids, amines, and peptides.Example in hormone diversity: several peptide hormones are heterodimers with a common ?Depending on the specific enzyme the cleavage may occur at different site of the peptide chain ?All peptide hormones synthesis is subjected to translational control.Complexity of hemostasis increase with increase life form; this need an increase in the number of hormones and increase in their diversity ?chain and the different ?–chain arise from a common duplicated ancestral gene (evolution).The evolution in hormone structure need evolution in its receptor for actions/ specificity spread.This provide a way for measuring regulatory control or the site of highest hormone availability.Steroid hormones are not stored in secreting cells.Synthesis is in the mitochondria of secreting cells from cholesterol.Some hormones are secreted in a pulsatile manner (pulses).o Understand the chemical nature of different classes of hormones and how this determines their mechanism of action on target cells.o Understand the principles governing disease states that result from over– or under–production of key hormones.TSH, FSH and LH: have same ?Synthesized initially as pre–pro–hormone ?The pre–pro–hormone cleave by specific proteases into pre–hormone ?The pre–hormone again cleave by specific proteases into the final hormone ?The hormone precursors are inactive.Activation of these receptors ended with expression of StAR protein.StAR traffics cholesterol

enter into the mitochondria ?Peptides are the most numerous.Peptides: by gene transcription ?Peptide hormones: ?The precursor is process inside a specific vesicles.The abundance of insulin level during meal can be explained.....They secreted by diffusion.The carrier expression is regulated by a gene.chain, with differ and specific ?–chain.This provide a genetic economy.??????????????????????????