ENDOCRINE BIOCHEMISTRY

LECTURE 1

Integration of Metabolism: Hormones & Cellular Signaling

Slide 1 | Integration of Metabolism: Hormones & Cellular Signaling

Integration of Metabolism, Hormones and Cellular Signaling The integration of metabolism with hormonal signaling is a core concept in physiology and biochemistry, as hormones are the primary regulators that coordinate the metabolic activities of different tissues to maintain **homeostasis**. Hormones are organic signaling molecules that are synthesized and secreted by specialized cells, transported through the bloodstream in very low concentrations, and exert their effects on distant target cells.

The term integration refers to the fact that no single hormone acts in isolation, rather, hormones work in complex networks, often with opposing or complementary actions, to fine-tune metabolic pathways such as **glycolysis**, **gluconeogenesis**, **lipogenesis**, and **protein synthesis**. Cellular signaling, on the other hand, is the process by which a hormone, carrying an extracellular signal, interacts with a receptor on or inside the target cell, triggering a cascade of intracellular events that ultimately produce a physiological response.

This integration is essential for survival, for example, during fasting, **glucagon** and **cortisol** mobilize energy stores, while **insulin** promotes storage after a meal. For medical students, understanding this integration is the key to comprehending **endocrine** disorders such as diabetes mellitus, thyroid dysfunction, and adrenal insufficiency, where the delicate balance of hormonal regulation is disrupted.

Moreover, many pharmacological agents target components of hormonal signaling pathways, making this knowledge directly applicable to clinical therapeutics.

Slide 3 | Outline

The first section covers fundamental concepts, the definition of a hormone, the principles of signaling, biochemical properties, the target cell concept, receptor domains, **signal amplification**, and regulation mechanisms. This foundational knowledge is essential because it establishes the vocabulary and conceptual framework that will be used throughout the rest of the course.

The second section delves into the structure, synthesis, and degradation of hormones, which is crucial for understanding how hormones are produced, stored, secreted, and cleared from the circulation, factors that directly influence their bioavailability and duration of action. The third and most extensive section addresses signal transduction, including second messengers, G-protein-coupled receptors, GPCRs, G-proteins, and adenylate cyclase.

These pathways represent the hardware through which the majority of hormonal signals are relayed from the extracellular environment to the intracellular machinery. The fourth section covers the phosquinositide cascade, calcium -binding proteins, and the receptor tyrosine kinase, RTK, cascade, which are essential for understanding growth factor signaling and **insulin** action.

Finally, the lecture series concludes with a section on steroidogenesis, which is covered as online material. This separation reflects the complexity of steroid hormone synthesis, which involves multiple enzymatic steps in specialized organs such as the adrenal cortex and gonads, and allows students to master the core concepts before tackling this more specialized topic.

By the end of this series, students should have a comprehensive understanding of how hormonal signals are generated, transmitted, amplified, and terminated, and how dysregulation of these processes leads to disease.

Slide 4 | Hormones: The Remote Controllers

Hormones are defined as organic molecules that are synthesized in minute quantities, transported via the bloodstream, and recognized by **specific** receptors on target cells. This definition distinguishes them from other signaling molecules such as neurotransmitters, which act over very short distances, synaptic clefts, and are rapidly degraded. Hormones can be categorized based on their mode of delivery.

Endocrine hormones are the classical type, they are secreted into the blood, travel over long distances, and are relatively stable in the circulation, allowing them to act on distant targets. The concentration of an **endocrine** hormone at its target is determined by the rate of secretion, the volume of distribution, and the rate of clearance.

Paracrine hormones act on neighboring cells without entering the systemic circulation, they are secreted into the interstitial fluid and affect cells in the immediate vicinity. An example is somatostatin, which is released from pancreatic delta cells and inhibits **insulin** and **glucagon** secretion from adjacent alpha and beta cells.

Autocrine hormones act on the same cell that secreted them, creating a self-regulatory loop that is particularly important in growth factor signaling and cancer biology, where **autocrine** loops can drive uncontrolled proliferation. The figure accompanying this slide likely illustrates these three modes of signaling, emphasizing the distance over which each type acts.

Understanding these distinctions is clinically relevant because many therapeutic strategies target paracrine or autocrine pathways, for example, somatostatin analogues are used to treat neuroendocrine tumors by inhibiting both endocrine and paracrine secretion.

Slide 5 | Nervous vs. Endocrine

The functional interrelationship between the nervous and endocrine systems becomes evident when we recognize that these two systems together regulate virtually all physiological processes. While they are often taught as separate entities, they are deeply interconnected, forming the **neuroendocrine** axis. The **hypothalamus**, for example, is a neural structure that secretes hormones, releasing and inhibiting factors that control the **pituitary** gland, effectively bridging the two systems.

The key difference between them is the speed and duration of their responses. The nervous system produces rapid, short-lived responses, measured in milliseconds, because it relies on action potentials that travel along axons and synaptic transmission at specialized junctions. The **endocrine** system, by contrast, produces slower but more prolonged responses, measured in minutes to days, because hormones must travel through the bloodstream and often require time to induce new **protein synthesis**.

Despite these differences, both systems may act simultaneously on the same target tissues, for example, the heart rate is regulated by both sympathetic nerves, rapid, and circulating **catecholamines**, sustained. Some nerve cells, known as neurosecretory cells, actually secrete hormones directly into the bloodstream, the posterior **pituitary** hormones, **oxytocin** and **ADH**, are classic examples of this neuro**endocrine** secretion.

Clinically, this integration is most evident in the stress response, where the sympathetic nervous system provides immediate fight-or-flight effects, while the hypothalamic pituitary adrenal, HPA, axis produces a slower but more sustained response through cortisol secretion. Understanding this interplay is essential for managing conditions like septic shock, where both neurogenic and endocrine dysfunction may contribute to hypotension, or in recovery from surgery, where the stress response must be carefully managed.

Slide 6 | The Target Cell Concept

Expanding the classical definition of a target cell to include any cell that possesses a receptor for a given hormone is essential, regardless of whether a biological response is actually observed. This is an important nuance because the presence of a receptor is a necessary but not sufficient condition for a response. The cell must also have the appropriate intracellular machinery, e.g., downstream effectors, second messenger systems, to transduce the signal.

The human body contains approximately 200 differentiated cell types, but only about 50 known hormones have been identified. Remarkably, all 75 trillion cells in the human body are targets for at least one hormone, and most cells are targets for multiple hormones. This creates a highly complex and interconnected signaling network.

One hormone can act on several different cell types, producing different effects in each, this is known as **pleiotropy**. For example, **cortisol** acts on the liver to increase **gluconeogenesis**, on adipose tissue to promote lipolysis, and on immune cells to suppress inflammation. Conversely, one cell type can respond to several different hormones, allowing for integration of multiple signals.

For instance, a hepatocyte receives signals from **insulin**, promoting storage, **glucagon**, promoting release, **epinephrine**, promoting release, and **cortisol**, promoting **gluconeogenesis**, and it integrates these signals to determine its metabolic state. This concept is fundamental to understanding **endocrine** physiology, as it explains why a single hormone can have such diverse effects and why **endocrine** disorders often present with multisystem manifestations.

It also underscores the importance of receptor expression and intracellular signaling components in determining tissue-**specific** responses to hormonal signals.

Slide 7 | Factors Affecting Hormone Concentration at the Target Cell

Multiple factors determine the concentration of a hormone available to bind to its receptor on the target cell, which is a critical determinant of the magnitude of the biological response. The first factor is the rate of synthesis and secretion of the hormone, which is regulated by feedback mechanisms, circadian rhythms, and physiological demands. For example, **cortisol** secretion follows a diurnal rhythm, peaking in the early morning, while **insulin** secretion is tightly coupled to blood glucose levels.

The second factor is the proximity of the target cell to the hormone source, **endocrine** hormones undergo dilution in the blood, whereas **paracrine** hormones achieve much higher local concentrations. The third factor is the dissociation constant, **Kd**, of the hormone-receptor complex, which reflects the **affinity** of binding. A lower **Kd**, higher **affinity**, means that the hormone can exert its effects at lower concentrations, making it more potent.

The fourth factor is the conversion of an inactive precursor to a fully active form, a process that occurs for many hormones. The most clinically significant example is the peripheral conversion of thyroxine, **T4**, to triiodothyronine, **T3**, by diiodinases in the liver and kidney. **T3** is several times more potent than **T4**, so this conversion is a crucial step in regulating thyroid hormone activity.

The fifth factor is the rate of clearance from the plasma, which is determined by the hormone's **half-life**. Peptide hormones typically have short half-lives, minutes, because they are rapidly degraded by proteases and cleared by the liver and kidneys, whereas steroid and thyroid hormones have long half-lives, hours to days, due to their association with carrier proteins.

This explains why peptide hormones must be given by continuous infusion or frequent injections, e.g., **insulin**, while thyroid hormones can be administered once daily. Medical students must appreciate these factors because they directly influence the

interpretation of hormone levels in clinical practice, e.g., total **T4** may be elevated due to increased binding proteins, but **free T4**, the active fraction, may be normal.

Slide 8 | Factors Affecting the Target Cell Response

On the other hand, other factors determine how a target cell responds to a given concentration of hormone. Even when the hormone concentration is optimal, the response can vary widely depending on the state of the target cell. The first factor is the number, relative activity, and occupancy of receptors on the cell surface. The number of receptors can change dynamically through **upregulation**, increased receptor synthesis, or **downregulation**, decreased receptor synthesis and increased degradation.

Downregulation occurs after prolonged exposure to high hormone concentrations and is a form of **desensitization** that protects the cell from overstimulation. This is clinically relevant in type 2 diabetes, where chronic hyper**insulin**emia leads to **downregulation** of **insulin** receptors, contributing to **insulin resistance**. The second factor is the metabolism of the hormone within the target cell, which may involve activation, e.g., conversion of testosterone to **dihydrotestosterone** by **5-alpha reductase** in the prostate, or inactivation, e.g., degradation of **CAMP** by **phosphodiesterase**.

The third factor is the presence of intracellular factors necessary for the response, such as second messenger molecules, kinases, or transcription factors. If these components are absent or dysfunctional, the cell may be unresponsive despite having functional receptors. The fourth factor is post-receptor **desensitization**, which involves the phosphorylation of the receptor or downstream signaling components, effectively uncoupling the receptor from its signaling pathway even when the hormone is still bound.

For example, phosphorylation of the beta-adrenergic receptor by GRKs, G-protein receptor kinases, promotes the binding of beta-restin, which leads to receptor internalization and reduced sensitivity. This is why chronic use of beta-agonists in asthma can lead to tachyphylaxis. Collectively, these factors explain why the same hormone concentration can produce different responses in different cells or in the same cell at different times, and they highlight the complexity of hormonal regulation beyond simple ligand-receptor binding.

Slide 9 | Receptors Discriminate Precisely

One of the most remarkable features of hormone -receptor interactions is the ability of receptors to discriminate between a hormone and structurally similar molecules despite enormous concentration differences. Hormones circulate in the blood at extremely low concentrations, typically in the atomolar to nanomolar range, 10^{-15}-10^{-9}M. In contrast, structurally related molecules, such as amino acids, sterols, and other metabolites, are present in the blood at micro- to millimolar concentrations, 10^{-6}-10^{-3}M, a difference of up to 10,000-fold or more.

For example, cortisol, a steroid hormone, circulates at 10 M, while cholesterol, its precursor, is present at 10^{-3}M. Despite this massive concentration disparity, the cortisol receptor can specifically bind cortisol without being activated by cholesterol or other related steroids. This specificity is achieved through the precise 3-dimensional architecture of the receptor's binding pocket, which is complementary in shape, charge, and hydrophobicity to the hormone.

The receptor uses a combination of hydrogen bonds, hydrophobic interactions, Van der Waals forces, and ionic bonds to recognize **specific** functional groups on the hormone. Any deviation in the molecular structure, even a subtle change in stereochemistry, can dramatically reduce binding **affinity**. This **specific**ity is the basis for pharmacological selectivity.

Drugs can be designed to mimic hormones and bind **specific**ally to their receptors without affecting other receptors. This is the principle behind highly selective beta -blockers, which block beta-1-adrenergic receptors without affecting beta-2 receptors. Understanding receptor **specific**ity is also clinically important because it explains why hormone assays are highly sensitive and **specific** and why hormone replacement therapy must be dosed precisely to avoid off-target effects.

Slide 10 | Hormone-Receptor Interactions

The key characteristics of hormone-receptor binding distinguish it from non-**specific** interactions. Hormone-receptor interactions are **specific**, meaning that the binding site is highly selective for the hormone or a class of structural analogs and can be competed for by **specific agonists** or **antagonists**. This **specific**ity allows for the development of drugs that can either mimic, **agonists**, or block, **antagonists**, the effects of endogenous hormones.

The interactions are also **saturable**, meaning that the number of receptors is finite. As the hormone concentration increases, a point is reached where all receptors are occupied and no further increase in response is possible, maximal response. This saturation phenomenon is described by the classic Michaelis-Menten-like binding curve.

The equilibrium dissociation constant, **Kd**, is defined as $\boldsymbol{Kd = (H \times R)/H - R}$,

where H is the **free** hormone concentration, R is the **free** receptor concentration, and H-R is the concentration of the hormone-receptor complex. The **Kd** represents the concentration at which 50 % of the receptors are occupied and is a measure of binding **affinity**.

A lower **Kd** indicates higher **affinity**, meaning that the hormone binds more tightly and can act at lower concentrations. For most hormones, **Kd** values range from 1 -0 to 1-0-1-1M, which corresponds to the physiological concentration range. At a hormone concentration equal to **20 times the Kd**, more than 95% of receptors are occupied, essentially achieving maximal binding.

This concept is clinically relevant because it explains why some patients with hormone resistance syndromes have normal hormone levels but reduced responses. For example, in androgen insensitivity syndrome, a mutation in the androgen receptor reduces its affinity for testosterone, increased Kd, resulting in impaired masculinization despite normal testosterone levels.

Slide 11 | Receptor Domains

The structural architecture of receptors reveals that all receptors have at least two functional domains, a **recognition domain** that binds the hormone, ligand, and a coupling or **signal transduction domain** that transmits the signal into the cell. The **recognition domain** is typically extracellular, for **cell surface receptors**, or within the ligand-binding pocket, for **intracellular receptors**. The coupling domain, by contrast, is intracellular, for **cell surface receptors**, or functions as the DNA binding and transcription activation domains, for **intracellular receptors**.

The process by which the receptor transduces the signal is known as receptor-effector coupling, and it occurs in two general ways. The first and most common involves changing the activity of an enzyme. This is the mechanism used by polypeptide hormones and **catecholamines**, which bind to receptors on the plasma membrane and activate intracellular enzymes such as **adenylyl cyclase** or **phospholipase C**.

The second mechanism is direct, in which the hormone-receptor complex itself acts as a transcription factor. This is used by **steroids**, thyroid hormones, and retinoids, which bind to **intracellular receptors**. These nuclear receptors have multiple functional domains, a hormone-binding site, a DNA-binding site, which recognizes **specific** sequences called **hormone response elements**, and binding sites for co-regulator proteins and cellular trafficking proteins.

The binding of the hormone induces a conformational change that allows the receptor to interact with co-regulators and regulate gene transcription. Receptor-effector coupling represents the first step in **signal amplification**, as one hormone molecule can activate many receptor molecules, each of which can activate multiple effectors. This modularity of receptor structure is a fundamental principle of molecular endocrinology and provides targets for drug development.

For example, selective estrogen receptor modulators, SERMs, bind to the estrogen receptor and can act as agonists in some tissues and antagonists in others, depending on the conformation they induce.

Slide 12 | Signal Amplification

The principle of **signal amplification** is a hallmark of hormonal signaling and the reason why hormones can be effective at extremely low concentrations. **Signal amplification** occurs at multiple steps along the signaling cascade, with each step multiplying the signal by several orders of magnitude. For example, when one molecule of **epinephrine** binds to a single **beta-adrenergic receptor**, it activates a G-protein, which in turn activates an **adenylyl cyclase** enzyme.

Each **adenylyl cyclase** molecule can catalyze the production of hundreds of **CAMP** molecules per second. Each **CAMP** molecule can activate a **protein kinase A**, pKa, molecule, and each pKa molecule can phosphorylate many target enzymes. The net amplification from a single hormone molecule can be 1-0 to 1-0-fold.

This explains why hormones secreted in picomolar or nanomolar concentrations can produce profound biological effects, such as the rapid mobilization of glucose during the stress response. Amplification also allows for a graded response, small changes in hormone concentration produce proportional changes in the downstream signal, enabling fine-tuned regulation.

However, amplification also carries a risk. If a component of the signaling pathway is dysregulated, e.g., a mutated G-protein that is constitutively active, the amplification cascade can produce massive and unregulated responses, leading to disease. This is seen in some **endocrine** tumors, such as growth hormone-secreting **pituitary** adenomas, where even a small tumor mass producing slightly elevated GH can cause **acromegaly** because the signal is amplified at every step.

For medical students, understanding amplification helps explain why hormone-secreting tumors cause such dramatic symptoms despite being small and why hormone replacement therapy requires precise dosing.

Slide 13 | How the Release Is Controlled?

Too little is ineffective, too much is dangerous. The principal mechanism by which hormone secretion is regulated is **feedback inhibition**. **Feedback inhibition** is a negative regulatory loop in which the product of a pathway inhibits its own production, maintaining **homeostasis**. There are three levels of feedback loops. The first is the **ultra-short loop**, in which a hormone inhibits its own secretion directly from the cell that produced it.

This is a rare but important mechanism. For example, ACTH can inhibit its own secretion from the **pituitary** corticotropes, providing a rapid, local control mechanism. The second is the **short loop**, in which a **pituitary** hormone feeds back to inhibit the secretion of its corresponding hypothalamic-releasing hormone. For example, **TSH** acts on the **hypothalamus** to inhibit **TRH** secretion.

The third and most clinically important is the **long loop**, in which a target gland hormone feeds back to inhibit both the **pituitary** and the **hypothalamus**. The classic example is the hypothalamic-**pituitary** thyroid axis. **TRH** from the **hypothalamus** stimulates **TSH** from the **pituitary**, which stimulates **T3** and **T4** from the thyroid gland.

T3 and **T4** then inhibit both **TRH** at the **hypothalamus** and **TSH** at the **pituitary** through **long loop** negative feedback. This system is remarkably precise, allowing thyroid hormone levels to be maintained within a narrow range despite fluctuations in dietary iodine and metabolic demand. Understanding these feedback loops is essential for interpreting **endocrine** laboratory tests.

For example, in primary hypothyroidism, failure of the thyroid gland T4 is low, TSH is elevated, because the lack of T4 removes the negative feedback on the pituitary, and TRH is also elevated. In secondary hypothyroidism, failure of the pituitary, both T4 and TSH are low, and TRH is elevated.

This pattern allows clinicians to localize the site of the lesion. Similarly, in **Cushing's disease**, **pituitary** ACTH secreting adenoma, **cortisol** is elevated, ACTH is elevated, or inappropriately normal, and the normal **feedback inhibition** is disrupted.

Slide 14 | Classification of Hormones

The various criteria used to classify hormones include chemical structure, solubility, receptor location, and the type of signaling mediator used. Chemical structure is the most useful and widely used classification because it correlates with other properties such as solubility, receptor location, and mechanism of action. The three major chemical classes are 1. small peptides, polypeptides, and proteins, which include the majority of hormones e.g., **insulin**, **glucagon**, ACTH, GH, 2.

amino acid derivatives, which include thyroid hormones **T3** and **T4**, and **catecholamines**, **epinephrine**, nor**epinephrine**, dopamine, and 3. **steroids**, which are derived from cholesterol and include glucocorticoids, mineralocorticoids, and sex **steroids**. A fourth class, arachidonic acid analogs, **eicosanoids**, are locally acting hormones that include prostaglandins, leukotrienes, and thromboxanes. This classification is clinically useful because it predicts the route of administration, duration of action, and mechanism of action.

Peptide hormones are **water-soluble** and cannot cross the cell membrane. They bind to **cell surface receptors** and act through second messengers. They must be given by injection, e.g., **insulin**, as they would be degraded in the gastrointestinal tract if taken orally. Steroid hormones are **lipid-soluble**, can cross the cell membrane, and bind to **intracellular receptors** that act as transcription factors.

They can be given orally, e.g., prednisone. Thyroid hormones are also **lipid-soluble** and bind to **intracellular receptors**, and they can also be given orally. **Catecholamines** are **water-soluble** and bind to **cell surface receptors**. They have very short half-lives and are given by injection or infusion. Understanding these differences is essential for clinical practice, as it dictates the choice of drug formulation and dosing schedule.

Slide 15 | Classification of Hormones - Chemistry & Transport

The transport mechanisms of the different hormone classes reveal important differences in their pharmacokinetics. Steroid hormones, being **lipid-soluble**, are hydrophobic and would not dissolve well in the aqueous plasma. To overcome this, they are transported bound to plasma proteins, such as corticosteroid-binding globulin, for **cortisol**, sex hormone-binding globulin, for androgens and estrogens, and albumin, for all **steroids**. Only the **free**, **unbound**, fraction is biologically active.

The bound fraction serves as a circulating reservoir that protects the hormone from rapid metabolism and provides a buffer against fluctuations in secretion. This is clinically important because conditions that alter binding protein concentrations, such as pregnancy, which increases thyroid-binding globulin and corticosteroid-binding globulin, or liver disease, which decreases **protein synthesis**, can affect total hormone levels without affecting **free**, active, hormone levels.

Thyroid hormones are also bound to **specific transport proteins**, including thyroxine-binding globulin, **TBG**, **transthyretin**, prealbumin, and albumin. **T4** is about 99. 97%bound to proteins, while **T3** is about 99. 7%bound, which partly explains why **T4** has a longer **half-life** than **T3**. Peptide hormones, by contrast, are **water-soluble** and dissolve readily in the blood, they generally do not require **specific transport proteins**, although some, such as **insulin**-like growth factors, do bind to **specific** carrier proteins, IGF-binding proteins, that regulate their bioavailability.

Catecholamines are also **water-soluble** and circulate in a **free** form, with a very short **half-life**, minutes. The binding of hormones to **transport proteins** not only increases their solubility and **half-life** but also provides a mechanism for tissue-**specific** delivery, as the dissociation of the hormone from its carrier can be regulated locally.

Slide 16 | Mechanism of Action - Intracellular Receptors

Hormones that bind to **intracellular receptors** include **steroids**, thyroid hormones, **T3** and **T4**, **calcitriol**, the active form of vitamin D, and **retinoic acid**. These hormones are all lipophilic, fat-soluble, and can cross the plasma membrane by simple diffusion because they are small and nonpolar. Once inside the cell, they bind to their **specific** receptors, which are located in the cytoplasm, for most steroid receptors, or in the nucleus, for thyroid hormone receptors and retinoid receptors.

The binding of the hormone induces a conformational change in the receptor, which causes it to dissociate from chaperone proteins, such as **heat shock proteins**, and, in the case of cytoplasmic receptors, translocate to the nucleus. In the nucleus, the hormone receptor complex binds to **specific** DNA sequences called **hormone response elements**, HREs, located in the promoter regions of target genes.

This binding recruits coactivators or core oppressors, which modulate the transcription of those genes, leading to either increased or decreased synthesis of **specific** proteins. Because this process involves new gene transcription and **protein synthesis**, the responses are slow, typically requiring hours to days to manifest fully. However, the effects are also long-lasting because the newly synthesized proteins can persist for extended periods.

This mechanism underpins many clinically important therapies, such as the use of glucocorticoids e. g., prednisone, for their anti-inflammatory effects, vitamin D analogs for osteoporosis, and thyroid hormone replacement for hypothyroidism. It also explains why these hormones cannot act rapidly in emergencies, unlike **catecholamines**, which act within seconds, and why their effects are difficult to reverse once they have been initiated.

Slide 17 | Mechanism of Action - Cell Surface Receptors

Hormones that bind to **cell surface receptors** are categorized according to the second messenger system they employ. All **water-soluble** hormones, peptides, **catecholamines**, and **eicosanoids** bind to receptors on the extracellular surface of the plasma membrane, as they cannot cross the lipid bilayer. The receptor transmits the signal to the intracellular side, where it activates a **specific** second messenger pathway. There are four main classes of second messenger pathways.

The first is the **CAMP** pathway, which is used by hormones such as beta- adrenergic **agonists**, **glucagon**, and ACTH. These hormones activate adenyl-L-cyclase-Bi-G proteins, increasing the production of **CAMP** from ADP. The second is the **CGMP** pathway, which is used by atrial natriuretic peptide, ANP, and **nitric oxide**, NO.

These hormones activate guanylyl cyclase, increasing the production of **CGMP** from GTP. The third is the calcium or phosphatidyl inositol pathway, which is used by hormones such as **oxytocin**, **TRH**, and angiotensin II, these hormones activate **phospholipase C**, generating IP3 and DAG, which increase intracellular calcium and activate protein kinase C.

The fourth is the kinase or phosphatase cascade pathway, which is used by hormones such as **insulin** and growth hormone. These hormones activate receptor tyrosine kinases, RTKs, or cytokine receptors that initiate phosphorylation cascades. The fact that many different hormones can use the same second messenger, for example, over 30 hormones use **CAMP**, raises the question of how the cell achieves **specific**ity. The answer lies in the concept of compartmentalization.

Different hormone receptors are localized in different microdomains of the plasma membrane, and the resulting pools of second messenger are spatially restricted. Additionally, different cell types express different downstream targets, so the same second messenger can produce different effects in different cells. This complexity is the basis for the remarkable **specific**ity of hormonal signaling despite the use of common messengers.

Slide 18 | General Features of Hormone Classes

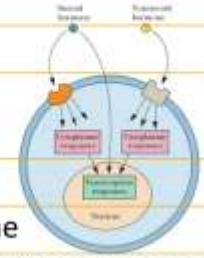
A comprehensive comparison between the two major classes of hormones, often referred to as group I, lipophilic, and group II, hydrophilic, reveals fundamental differences in their properties. Group I hormones include **steroids**, iodothyronines, thyroid hormones, **calcitriol**, and retinoids. These hormones are lipophilic, meaning they can cross the plasma membrane and bind to **intracellular receptors**. Their mechanism of action is slow because it involves gene transcription and **protein synthesis**, but their effects are long-lasting due to the persistence of the newly synthesized proteins. They are transported in the blood bound to carrier proteins,

which extends their **half-life** from hours to days. Group 2 hormones include polypeptides, proteins, glycoproteins, and **catecholamines**. These hormones are hydrophilic, **water-soluble**, and cannot cross the plasma membrane; they bind to receptors on the cell surface. Their mechanism of action is fast because it involves second messengers and post- translational modifications, which can occur within seconds to minutes.

However, their effects are short-lived because the second messengers are rapidly degraded and the hormones are cleared from the circulation quickly. They are transported dissolved in the plasma and generally do not require carrier proteins, which contributes to their short **half-life**, minutes. The table also highlights that the receptor for group I hormones is intracellular, and the mediator is the hormone receptor complex itself acting as a transcription factor.

In contrast, group 2 hormones have plasma membrane receptors, and the mediators are second messengers such as **CAMP**, **CGMP**, Ca superscript 2, or kinase cascades. This classification is fundamental to endocrinology and has profound implications for pharmacology, for example, a group 2 hormone like **insulin** must be given by injection because it would be digested if given orally, whereas a group I hormone like **cortisol** can be given orally because it is not destroyed in the gastrointestinal tract.

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor- hormone	cAMP, cGMP, Ca^{2+}, kinase cascades,



Slide 19 | Genomic Responses vs. Rapid Responses

A critical nuance in endocrinology is that the traditional dichotomy between slow **genomic** responses and fast **non-genomic** responses is not absolute. While it is true that steroid and thyroid hormones predominantly act through nuclear receptors to regulate gene transcription, **genomic** responses, it is now well established that these same hormones can also elicit rapid effects through membrane-bound receptors or receptor variants, **non-genomic** or rapid responses.

The table provided in the slide illustrates several examples. For thyroid hormone, **T3**, the **genomic** response occurs when **T3** binds to its nuclear receptor, TR-beta, leading to the dissociation of core oppressors and recruitment of coactivators, which modulates transcription. However, **T3** can also activate PI3 kinase and **MAP kinase** pathways, rapid responses, within minutes, leading to effects such as glucose uptake and activation of Ca superscript 2 ATPase.

Similarly, vitamin D, **calcitriol**, has a well-known **genomic** effect of increasing intestinal calcium absorption by inducing the synthesis of calcium-binding proteins, CABP. but it also has rapid, **non-genomic** effects, such as opening chloride channels in osteoblasts and keratinocytes within 20 minutes, as well as stimulating **insulin** secretion from beta cells. Estrogen can act through its nuclear receptors, R and R, to regulate ovarian function, but it can also activate **PI3K**-slash-ACT signaling through membrane-bound R, leading to rapid **nitric oxide** release.

Cortisol, the primary glucocorticoid, is essential for life, knockout of the glucocorticoid receptor is lethal at birth, but it can also stimulate **PI3K**-ACT to release NO in seconds. Aldosterone, progesterone, and androgens all show similar dual modes of action. This dual signaling has important clinical implications. For example, some of the beneficial effects of **steroids**, such as the rapid anti-inflammatory actions of glucocorticoids, may be mediated through **non-genomic** pathways, which has led to the development of drugs that can selectively target either **genomic** or **non-genomic** pathways. It also explains why some effects of **steroids** occur much faster than can be accounted for by transcription, and why certain steroid analogs have differing profiles of efficacy and side effects.

responses

(Steroid receptor) & ligand	# aa Receptor	Steroid nuclear receptors & gene transcription generate genomic responses (GR)	Steroid membrane receptors generates rapid responses (RR)
(Thyroid β) T_3	461	T_3 binding to its nuclear receptor, in target cells stimulates dissociation of co-repressors, recruitment of co-activators, etc. to complete a GR.	T_3 activates PI3kinases and MAP kinase **RR** pathways which can result in glucose uptake, Ca^{2+}-ATPase, Na^+/H^+ antiporter.
(Vitamin D receptor) $1\alpha,25(OH)_2$- vitamin D_3	427	Both intestinal Ca^{2+} absorption & kidney Ca^{2+} reabsorption requires **GR** for production of new calcium binding proteins (CaBP).	**RR** opening of Cl^- channels in osteoblasts & keratinocytes in 20 min; insulin secretio from β-cells, MAP kinase activation in NB cells.
(Estrogen receptor α) Estradiol	595	ERα **GR** are required for normal ovarian function.	ERα activates PI3K and then AKt **RR** stimulates nitric oxide NO.
(Estrogen receptor β) Estradiol	530	ERβ **GR** are required for ovulation & pregnancy.	The cell membrane ERβ bound to caveola has been implicated in RR.
(Glucocorticoid receptor) Cortisol	777	Knockout (KO) of the mouse GC receptor is lethal at time of birth.	Cortisol stimulates PI3-kinase/Akt to activate in seconds NO release.
(Mineralocorticoid receptor) Aldosterone	919	MR **KO** mice die of Na^+ and H_2O deprivation.	Aldosterone activates in 3–15 minutes the **RR** of Na^+/H^+ exchange in renal cells.
(Progesterone receptor) Progesterone	933	The progesterone receptor participates in **GR** sexual differentiation determination.	Progesterone stimulates **RR** within second to minutes, the acrosome reaction in spermatozoa.
(Androgen receptor) Testosterone	919	**KO** of the AR male mouse causes development of female genitalia.	Activation of MAP kinase then activates t ERK pathway via **RR**.

End of Lecture 1