

# Adrenocorticotrophic Hormone (ACTH)

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## Adrenocorticotrophic Hormone (ACTH)

**Primary Disciplinary Field(s):** Endocrinology, Physiology

### 1. Core Definition

The **Adrenocorticotrophic Hormone (ACTH)**, often referred to as corticotropin, is a vital peptide hormone synthesized and secreted by the corticotroph cells within the **anterior pituitary gland** (anterior pituitary gland). This hormone serves as the primary regulatory signal for the production and release of **glucocorticoids** (glucocorticoids), notably **cortisol** (cortisol), from the adrenal cortex. The significance of ACTH lies in its direct control over the body's physiological response to stress, its influence on metabolic processes, and its modulation of immune function, effectively integrating these systemic responses.

ACTH is fundamentally integrated into the **Hypothalamic-Pituitary-Adrenal (HPA) axis** (HPA axis), a sophisticated neuroendocrine feedback loop critical for maintaining systemic homeostasis and adapting to internal and external stressors. The synthesis of ACTH is initiated by the cleavage of a larger precursor molecule, **proopiomelanocortin (POMC)** (proopiomelanocortin), which undergoes complex post-translational modifications. This processing yields ACTH alongside other crucial biologically active peptides, including melanocyte-stimulating hormone (MSH) and  $\beta$ -endorphin, demonstrating its broad regulatory potential originating from a common source.

The regulatory cascade begins in the hypothalamus, which releases **corticotropin-releasing hormone (CRH)** (CRH) in response to stress or other systemic stimuli. CRH then targets the pituitary, stimulating the prompt secretion of ACTH into the bloodstream. Upon reaching the adrenal cortex, ACTH exerts its effect by binding specifically to melanocortin 2 receptors (MC2R) on the surface of adrenal cells. This binding activates a subsequent intracellular signaling cascade that drives the synthesis and liberation of adrenal steroids, thus completing the central mechanism of the HPA axis response and ensuring the appropriate physiological output.

### 2. Etymology and Historical Development

The historical investigation into ACTH is deeply intertwined with the development of modern endocrinology, commencing in the early decades of the 20th century. The initial conceptualization of a pituitary factor responsible for stimulating the adrenal cortex arose during the 1930s, based on observed physiological dependencies between the glands. This period of intense research was driven by the desire to understand how the body mediated its vital stress reactions and maintained metabolic stability, hypothesizing a humoral link between the central nervous system and the peripheral endocrine glands.

A pivotal breakthrough occurred in the 1950s when scientists achieved the successful isolation and

precise chemical characterization of ACTH. This milestone provided the necessary structural and functional clarity to fully appreciate its role as corticotropin. This chemical isolation was crucial, enabling the subsequent development of highly sensitive diagnostic methodologies capable of accurately measuring circulating ACTH levels in patients. Such measurements quickly became an indispensable tool for diagnosing and managing a variety of complex endocrine disorders, allowing clinicians to distinguish between primary and secondary adrenal dysfunction.

The rigorous research focusing on ACTH and its central position in the HPA axis dramatically expanded the scientific community's understanding of stress physiology, immunological modulation, and systemic metabolic regulation. Furthermore, this knowledge base facilitated significant clinical advancements, particularly the creation of synthetic ACTH analogs, such as cosyntropin. These analogs are routinely employed today in clinical settings to specifically test the functional capacity of the adrenal gland, confirming the lasting clinical legacy of ACTH research. Continuous progress in molecular biology and hormonal research continues to refine the understanding of the intricate mechanisms governing ACTH synthesis, secretion kinetics, and specific cellular actions, providing ever-deeper insights into endocrine pathophysiology.

### 3. Key Characteristics

ACTH exhibits several defining characteristics that underscore its indispensable role in endocrine regulation and stress response mechanisms. These characteristics dictate how the hormone is synthesized, released, and functions within the body's complex feedback systems, ensuring dynamic and adaptive responses to physiological needs.

**Regulation of Glucocorticoid Synthesis:** ACTH functions as the unequivocal primary signaling molecule governing the biosynthesis of glucocorticoids within the adrenal cortex. Its specific interaction with MC2R receptors catalyzes the enzymatic pathways necessary for the rapid production and subsequent secretion of essential hormones like cortisol, thereby ensuring timely systemic responses to physiological demands for energy mobilization and anti-inflammatory activity.

**Diurnal and Ultradian Rhythmicity:** ACTH secretion is characterized by a pronounced **diurnal rhythm**, a pattern synchronized fundamentally with the sleep-wake cycle and modulated by external cues such as light exposure and feeding habits. Typically, ACTH concentrations peak during the early morning hours, preparing the organism for the daily activity cycle, and reach their nadir in the late evening. This temporal pattern reflects the inherent need for dynamic hormonal regulation throughout the day, often exhibiting superimposed ultradian pulses.

**Central Role in the Stress Response:** ACTH occupies a central and non-negotiable position within the body's neuroendocrine **stress response** pathway. Upon encountering a significant internal or external stressor, the hypothalamic release of CRH rapidly triggers the pituitary to secrete ACTH. This immediate surge in ACTH subsequently stimulates the adrenal cortex to

release a corresponding surge of cortisol. Cortisol, in turn, facilitates the body's adaptive coping mechanisms by mobilizing energy reserves, suppressing excessive inflammation, and tempering immune responses, thus resolving the acute stress phase.

#### 4. Significance and Impact

The physiological significance of ACTH cannot be overstated, given its critical function in orchestrating the body's homeostatic responses and its pivotal role in regulating the complex interplay between the nervous and endocrine systems. Its widespread influence spans essential physiological domains, including systemic metabolism, immune competency, and precise cardiovascular regulation, making it a foundation of systemic hormonal stability and adaptability.

Disruptions or imbalances in the secretion profile of ACTH are directly responsible for causing a spectrum of severe endocrine disorders, demonstrating the hormone's necessity for health. One such disorder is **Cushing's disease** (Cushing's disease), which typically arises from excessive, unregulated production of ACTH, often secondary to a benign pituitary tumor (corticotropinoma). This pathological hypersecretion leads to chronic hypercortisolism, resulting in characteristic symptoms such as central obesity, muscle wasting, and hypertension, carrying high morbidity if untreated.

Conversely, inadequate or deficient production of ACTH results in secondary **adrenal insufficiency** (adrenal insufficiency). This condition is marked by critically decreased levels of cortisol, leading to debilitating symptoms including profound fatigue, persistent muscle weakness, unexplained weight loss, and potentially life-threatening adrenal crises under duress. Due to its diagnostic utility, specialized ACTH stimulation tests, which gauge the adrenal gland's responsiveness to administered ACTH, are routinely employed in clinical endocrinology to meticulously assess the functional reserve of the adrenal glands and determine the root cause of suspected adrenal insufficiency.

#### 5. Debates and Criticisms

Despite decades of established research regarding ACTH's primary function, the hormone and its associated regulatory pathways remain areas of active scientific investigation and debate. A central area of contention focuses on the precise and highly nuanced mechanisms that modulate ACTH secretion dynamics and the multitude of factors that influence the overall reactivity and sensitivity of the HPA axis. While CRH is confirmed as the primary and most potent stimulator of ACTH release, ongoing research continues to explore the contributions of various ancillary neuropeptides, neurotransmitters, and circulating cytokines that may fine-tune or override the CRH signal, particularly during chronic stress or inflammatory states.

Another significant area of debate revolves around the optimal clinical deployment and therapeutic

profile of synthetic ACTH analogs. Although these synthetic compounds have historically been utilized for the management of various severe inflammatory and certain autoimmune conditions, their comparative efficacy and long-term safety profiles, particularly when weighed against modern, targeted immunomodulatory treatments, remain subjects of rigorous clinical scrutiny. Some emerging scientific data suggest that ACTH may possess certain non-specific anti-inflammatory effects that operate independently of its classic steroidogenic action on the adrenal cortex. This potential dual mechanism of action raises complex questions about the true breadth of its therapeutic utility and how it should be optimally integrated into contemporary clinical protocols for non-endocrine disorders.

## 6. Further Reading

[Adrenocorticotrophic hormone \(ACTH\)](#)

[Hypothalamic-pituitary-adrenal \(HPA\) axis](#)

[Cortisol and Glucocorticoids](#)

[Corticotropin-releasing hormone \(CRH\)](#)

[Cushing's disease](#)

[Adrenal insufficiency](#)