

# ADRENOCORTICOTROPIC HORMONE (ACTH)

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## ADRENOCORTICOTROPIC HORMONE (ACTH)

**Primary Disciplinary Field(s):** Endocrinology, Neuroendocrinology, Physiological Psychology

### 1. Core Definition

The **Adrenocorticotrophic Hormone (ACTH)**, frequently known by the synonymous term **corticotrophin**, is a vital polypeptide hormone produced and secreted by the anterior lobe of the pituitary gland. ACTH acts as a primary messenger within the endocrine system, specifically targeting the adrenal glands. Its fundamental physiological role is to manage and stimulate the regular production and dispersion of **steroid chemicals**, primarily the glucocorticoids like cortisol, originating from the adrenal cortex. The regulation of this hormone is critical for maintaining homeostasis, particularly during periods of physiological stress or fluctuation in circadian rhythms. ACTH secretion is not constant but occurs in distinct pulses, following a diurnal rhythm that generally peaks in the early morning hours and declines late in the evening. This pattern ensures that the body is prepared for the metabolic demands of waking and activity.

ACTH functions as the crucial link between the central nervous system and the peripheral endocrine response system, establishing the regulatory cascade known as the Hypothalamic-Pituitary-Adrenal (HPA) axis. The hormone's actions are strictly controlled by negative feedback mechanisms, ensuring that the levels of circulating glucocorticoids remain within a tight physiological range. Any disruption to the synthesis, secretion, or reception of ACTH--whether due to pathology in the pituitary gland, hypothalamus, or adrenal cortex--can lead to severe systemic imbalances, affecting metabolism, immune function, and neurobehavioral states. Given its powerful regulatory role over stress hormones, ACTH is of profound significance in both clinical medicine and physiological psychology, where its concentration is often measured to diagnose various endocrine disorders.

### 2. Molecular Structure and Synthesis

ACTH is a relatively small peptide hormone, consisting of 39 amino acids. However, its origin is traced back to a much larger, complex precursor protein known as **proopiomelanocortin (POMC)**. POMC is synthesized in the corticotroph cells of the anterior pituitary gland, as well as in specific neurons within the hypothalamus and brainstem. The synthesis and processing of POMC are highly regulated, involving enzymatic cleavage by prohormone convertases. Depending on the tissue where POMC is processed, different biologically active peptides are generated. In the anterior pituitary, the primary cleavage products include ACTH, N-terminal peptide, and beta-lipotropin.

The bioactivity of ACTH resides primarily within its N-terminal sequence, specifically the first 24

amino acids, which are responsible for stimulating corticosteroid production. The remaining C-terminal sequence, while less critical for adrenal stimulation, ensures the stability and full biological efficacy of the hormone. The synthesis rate of POMC, and consequently ACTH, is dynamically regulated by signals originating from the hypothalamus. Most notably, the release of **corticotropin-releasing hormone (CRH)** from the paraventricular nucleus of the hypothalamus acts as the principal positive stimulus, dramatically increasing the transcription and translation of the POMC gene in the pituitary cells, thereby preparing the system for a robust stress response.

Once synthesized, ACTH is stored in secretory granules within the corticotroph cells, awaiting the stimulus from CRH. The release mechanism is rapid; upon binding of CRH to its receptors on the pituitary cell membrane, an intracellular signaling cascade, involving cyclic adenosine monophosphate (cAMP), triggers the immediate exocytosis of ACTH into the bloodstream. This pulse release allows for swift communication between the central nervous system and the adrenal glands, which is essential for managing immediate physiological demands, such as fight-or-flight responses.

### 3. Physiological Function and Mechanism of Action

The primary target of ACTH is the adrenal cortex, the outer layer of the adrenal gland. The adrenal cortex is histologically and functionally divided into three zones: the zona glomerulosa (producing mineralocorticoids), the zona fasciculata (producing glucocorticoids), and the zona reticularis (producing androgens). ACTH exerts its most powerful influence over the **zona fasciculata** and the **zona reticularis**. Upon reaching the adrenal gland via the bloodstream, ACTH binds to specific high-affinity G-protein coupled receptors, primarily the melanocortin 2 receptor (MC2R), located on the surface of the adrenal cortical cells.

The binding of ACTH initiates a complex intracellular signaling pathway, predominantly utilizing the second messenger system involving **cAMP**. Elevated intracellular cAMP levels activate Protein Kinase A (PKA), which then phosphorylates several key regulatory enzymes involved in steroidogenesis. The critical action of ACTH is the stimulation of the conversion of cholesterol, the precursor molecule, into steroid hormones. A rate-limiting step in this process is the transport of cholesterol into the inner mitochondrial membrane, a process mediated by the Steroidogenic Acute Regulatory protein (StAR). ACTH significantly upregulates StAR expression and activity, thereby ensuring a ready supply of substrate for steroid production.

The most significant output resulting from ACTH stimulation is the secretion of **cortisol**, the main human glucocorticoid. Cortisol plays expansive roles throughout the body, including regulating metabolism (promoting gluconeogenesis), suppressing inflammation, and modulating immune responses. ACTH also stimulates the secretion of adrenal androgens from the zona reticularis, although its control over mineralocorticoids (like aldosterone, produced in the zona glomerulosa) is

minimal, as aldosterone secretion is primarily regulated by the renin-angiotensin-aldosterone system. This targeted stimulation highlights ACTH's specialization in managing stress and energy balance.

#### 4. Role in the Hypothalamic-Pituitary-Adrenal (HPA) Axis

ACTH serves as the central operative component of the **Hypothalamic-Pituitary-Adrenal (HPA) axis**, which is the body's major neuroendocrine system governing the adaptive response to stress. The HPA axis operates through a tightly regulated hierarchy and feedback loop designed to maintain physiological stability. The cascade begins in the hypothalamus, which perceives internal and external stressors (e.g., trauma, infection, fear, hypoglycemia). In response, the hypothalamus releases CRH into the hypophyseal portal system, which then travels to the anterior pituitary.

Upon receiving the CRH signal, the anterior pituitary immediately releases ACTH into the systemic circulation. ACTH then travels to the adrenal cortex, triggering the rapid release of cortisol. Cortisol's subsequent systemic effects are manifold, mobilizing energy stores and preparing the body for action. Once sufficient levels of cortisol are achieved in the bloodstream, the system initiates a powerful negative feedback loop. Cortisol acts on glucocorticoid receptors located in both the hypothalamus and the anterior pituitary, inhibiting the further release of CRH and ACTH, respectively.

This sophisticated feedback mechanism is essential for preventing the harmful effects of prolonged exposure to high levels of stress hormones. If the HPA axis were unregulated, chronic elevation of cortisol would lead to severe metabolic and immune dysfunction. Thus, ACTH acts as the metronome of the axis; its secretion rate dictates the magnitude and duration of the stress response, ensuring that hormone release is proportional to the perceived threat and is quickly curtailed once the immediate danger has passed or metabolic needs are met.

#### 5. Clinical Relevance: Deficiency and Overactivity

Dysregulation of ACTH levels, whether due to primary pituitary failure or secondary adrenal issues, results in significant clinical pathology, impacting overall physiological health and psychological well-being. The source content explicitly notes that **overactivity of the adrenocorticotrophic hormone** may lead to disproportionate parts of the body, physiological side effects, and altered mood states. This condition, where there is excessive secretion of ACTH, is known as ACTH-dependent hypercortisolism, or **Cushing's Disease** if the cause is a pituitary tumor (adenoma).

In Cushing's Disease, persistent, high levels of ACTH overstimulate the adrenal cortex, leading to chronic cortisol excess. Clinical manifestations include profound metabolic disruptions: central obesity, accumulation of fat pads (such as the "buffalo hump"), muscle wasting in the limbs leading to the "disproportionate parts" mentioned, thinning of the skin, and hypertension. Physiologically,

patients often experience immune suppression and hyperglycemia. Furthermore, the accompanying mood changes--ranging from enhanced euphoria and irritability to severe diminished mood, anxiety, and depression--are significant psychological side effects directly linked to the excessive corticosteroid load regulated by ACTH.

Conversely, **ACTH deficiency** results in secondary adrenal insufficiency, where the adrenal cortex is healthy but lacks the necessary ACTH stimulation. Causes often include damage to the pituitary (e.g., Sheehan's syndrome) or, more commonly, prolonged administration of exogenous glucocorticoids which suppress native ACTH release. Symptoms of deficiency include chronic fatigue, severe hypotension, hypoglycemia (due to lack of cortisol-mediated gluconeogenesis), and general malaise. Unlike primary adrenal insufficiency (Addison's disease), ACTH deficiency does not typically result in hyperpigmentation, as the melanocyte-stimulating portions of POMC are not excessively produced.

## 6. Psychological and Behavioral Effects

While ACTH's primary established function is hormonal stimulation, emerging research suggests that ACTH, or its related peptide fragments, may possess direct neuromodulatory activity within the central nervous system, independent of its cortisol-releasing function. This is supported by the fact that the POMC precursor is synthesized in various brain regions, and ACTH receptors have been identified in specific areas related to cognition and emotion. The source material's mention of **enhanced or diminished mood** strongly aligns with ACTH's broader role in stress coping and neuropsychological function.

ACTH and its fragments, particularly ACTH (4-10), have been implicated in influencing cognitive processes, including attention, arousal, and memory consolidation. Studies indicate that ACTH may help sustain attention and improve vigilance, particularly under stressful conditions. Furthermore, the dysregulation of ACTH is centrally involved in the pathophysiology of various mood and anxiety disorders. Chronic stress, leading to persistent CRH and ACTH elevation, is a significant risk factor for major depressive disorder and post-traumatic stress disorder (**PTSD**). The inability of the HPA axis to properly implement negative feedback--often manifesting as high basal ACTH or cortisol levels--is a biomarker of chronic stress and contributes directly to the affective side effects noted in clinical hypercortisolism.

## 7. Further Reading

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

[Physiology, Adrenocorticotrophic Hormone \(ACTH\) - StatPearls \(NCBI Bookshelf\)](#)

[Proopiomelanocortin \(POMC\) - ScienceDirect](#)

[The Hypothalamic-Pituitary-Adrenal Axis and Major Depressive Disorder: A Review](#)