

Mini Review

Anterior Pituitary Gland: Adrenocorticotrophic Polypeptide Hormone Analysis

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Citation: Andersen E, Sbardella T, Benjamins Y, Lisak R, Giordano T, Kiwaki J, Valeriano G, Mattos T, Anterior Pituitary Gland: Adrenocorticotrophic Polypeptide Hormone Analysis V1(2),2025

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Received date: September 30, 2025; Accepted date: October 18, 2025; Published date: October 29, 2025

Keywords: hypothalamic–pituitary–adrenal axis, reproductive systems, mineralocorticoids, corticotrophin

Abstract

Adrenocorticotrophic hormone (ACTH) is a tropic hormone produced by the anterior pituitary. The hypothalamic-pituitary axis controls it. ACTH regulates cortisol and androgen production. Diseases associated with ACTH include Addison disease, Cushing syndrome, and Cushing disease. ACTH secretion is characterized by pulsatile release of ACTH from the corticotroph in a burst-like pattern, with no interpulse secretion [154]. Fifteen-minute sampling reveals approximately 12 ACTH and cortisol pulses over a 24-hour period, whereas more frequent 10-minute sampling reveals 40 ACTH pulses in 24 hours [154]. Blood ACTH rises by an average of 24 pg/ml per pulse [154]. β -endorphin secretion parallels the pulsatile release of ACTH.

Introduction

Adrenocorticotrophic hormone (ACTH) was first described in 1933, and after nearly 20 years, it was demonstrated that this polypeptide hormone stimulates adrenocortical activity. ACTH is exclusively produced from prohormone proopiomelanocortin (POMC), which is majorly synthesized in the corticotroph and melanotroph cells of the anterior and intermediate lobes of the pituitary gland and the arcuate nucleus of the hypothalamus. ACTH synthesis has also been described in other organs, such as the skin. After synthesis and folding, POMC is transported in vesicles and processed in secretory granules before ultimately reaching the plasma membrane. The selective cleavage of POMC by prohormone convertase (PC) and the timing of secretion are cell-specific and follow the regulated secretory pathway, along with other hormones because of a highly conserved sorting signal motif. In immature secretory granules, PC1/3 and PC2 enzymes process POMC.

After its cleavage from POMC by PC1/3, ACTH is secreted by mature granules from the anterior lobe of the pituitary gland into the circulation, targeting its receptor on peripheral cells, the melanocortin 2 receptor (MC2R). In addition to MC2R, which is highly specific for ACTH, other melanocortin receptors (MCRs; MCR1, MCR3, MCR4, and MCR5) can bind to ACTH and other POMC-derived peptides. These receptors are expressed in various tissues. Similar to other GPCRs, MC2R activation leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) stimulating the protein kinase A (PKA) signaling pathway. Other intracellular pathways activated by ACTH are mitogen-activated protein kinase and cAMP response element-binding protein. A role of calcium influx that cooperates with ACTH-mediated steroid synthesis has also been identified, and many other secondary messengers are involved in ACTH downstream signaling, although their independence from the PKA pathway is still under discussion. The interaction between MC2R and ACTH in the adrenal glands leads to transcription of genes responsible for steroidogenesis, such as the steroidogenic acute regulatory protein (StAR).

Adrenal Effects of ACTH
Corticosteroid Rhythmicity

It is well established that circadian changes in ACTH and glucocorticoids are associated with expression of clock-related genes. In adrenal tumors, the clock machinery that mitigates the response to ACTH and stress favors a higher and more arrhythmic corticosteroid secretion when dysregulated, suggesting that hypercortisolism exerts effects on circadian genes, contributing to the worsening of disease-related comorbidities.

Effects on Steroidogenesis

ACTH is the key hormone controlling steroidogenesis in the adrenal gland, inducing responses in both the short and long terms. Acute and chronic ACTH stimulation lead to the mobilization of cholesterol, the first substrate for steroidogenic pathway, owing to the increase in StAR gene transcription. StAR catalyzes the conversion of cholesterol to pregnenolone, the first and limiting step of steroidogenesis.

Different exposures to ACTH might affect aldosterone production differently; in fact, under continuous intravenous ACTH infusion aldosterone increases and then returns to basal levels within 72 hours, but pulsatile administration of ACTH, which mimics its physiological release, causes aldosterone to remain at high levels. However, most results on strong aldosterone stimulation by ACTH are limited to *in vitro* studies while evidence from animal models suggest an inhibitory effect of Angiotensin II signaling on cAMP and Ca²⁺ intracellular cascades, that are activated by ACTH binding to MC2R, thus dampening the *in vivo* effects on mineralocorticoid secretion.

Effects Against Reactive Oxygen Species

ACTH-induced steroidogenesis reactions involve lipid peroxidation and production of reactive aldehyde metabolites that generate reactive oxygen species (ROS) and thus a considerable cellular oxidative stress. Consequently, several enzymes involved in the detoxification are mobilized in adrenal cells. Aldo-keto reductases participate into this detoxification process, and their expression is ACTH-dependent. Moreover, in human and rat adrenal cells, seladin-1 (selective Alzheimer disease indicator 1, also named 24-dehydrocholesterol reductase) expression and redistribution to the nucleus occur after ACTH treatment.

Effects on Adrenal Growth and Adrenal Blood Flow

An *in vitro* study showed that ACTH leads to increased cell death through the apoptosis of isolated cells in cultures of the adrenal cortex; however, the zona fasciculata and zona reticularis are more resistant to the cytotoxic and antimitogenic effects of ACTH than zona glomerulosa. In contrast with these results, in animal models, ACTH regulates adrenal gland trophicity and increases adrenal blood flow. Furthermore, glucocorticoid-induced suppression of ACTH inhibits cell proliferation, induces apoptosis, decreases adrenal weight and cellularity of the adrenal cortex, and triggers vascular changes through loss of vascular endothelial growth factor protein expression, thereby causing regression of the vascular network. Moreover, knockout of the MC2R gene in mice leads to marked atrophy of the zona fasciculata and high levels of MC2R expression in the undifferentiated zone, which contains stem cells supports the notion that ACTH may play an important role in adrenal cell differentiation

and the importance of the ACTH-MC2R complex in adrenal development.

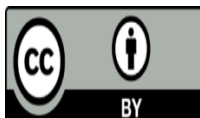
Conclusion

The role of ACTH in maintaining adrenal homeostasis and participating in the HPA axis is self-evident. However, after an initial number of studies on its potential as a therapeutic strategy in many diseases and conditions, researchers seem to have abandoned the “corticotropin path” and have focused more on its downstream hormone pathways (glucocorticoids and androgens).

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Journal of Endocrinology, Diabetes and Metabolic Complications (JEDMC)



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