Multiple Signaling Pathways Coordinate CYP17 Gene Expression in the Human Adrenal Cortex

Marion B. Sewer*, Donghui Li, Eric B. Dammer, Srinath Jagarlapudi and Natasha Lucki

School of Biology and Parker H. Petit Institute for Bioengineering & Biosciences,
Georgia Institute of Technology, Atlanta, GA 30332-0230

* *Corresponding author: marion.sewer @biology.gatech.edu*

Abstract

Optimal levels of steroid hormone biosynthesis are assured by the integration of several regulatory mechanisms, including substrate delivery, enzymatic activity, and gene transcription. In the human adrenal cortex, optimal glucocorticoid secretion is achieved by the actions of adrenocorticotropin (ACTH), which exerts transcriptional pressure on all genes involved in steroidogenesis. One of these genes is *CYP17*, which encodes P450 17α-hydroxylase-17,20 lyase, a key enzyme in the production of cortisol and adrenal androgens. Levels of *CYP17* transcription are regulated by multiple regulatory mechanisms that act to respond to various signaling cues. These cues are coordinated in a developmental, species-, and tissue-specific manner, with an additional time/circadian-dependent level of regulation. This brief review will highlight some of the signal transduction cascades and transcription factors that have been shown to modulate *CYP17* gene expression in the adrenal cortex.

Keywords: CYP17, adrenocorticotropin, angiotensin II, cAMP, steroid hydroxylase, steroidogenic factor-1, PKA

1. Overview

Steroid hormones exert control of diverse physiological processes by serving as ligands for intracellular and plasma membrane receptors. While ligand binding to plasma membrane receptors is coupled to the rapid activation of signaling pathways, hormone-bound intracellular receptors are transcription factors, and thus alter gene expression by binding to DNA response elements. Cortisol, aldosterone, and adrenal androgens are the primary bioactive steroid hormones that are produced in the human adrenal cortex. Like all classes of steroid hormones, biosynthesis occurs in a multi-step process and requires the actions of both members of the cytochrome P450 monooxygenase superfamily, as well as hydroxysteroid dehydrogenases. These enzymes catalyze the conversion of cholesterol to aldosterone, cortisol, or adrenal androgens in a zone-specific manner. Aldosterone, a mineralocorticoid, is a key regulator of sodium and potassium homeostasis and is produced in the zona glomerulosa, whereas adrenal androgens are synthesized in the zona reticularis. The glucocorticoid cortisol directs carbohydrate metabolism, as well as modulates blood pressure and the immune response, and is produced in the zona fasciculata. This review will focus on the transcriptional regulation of *CYP17*. CYP17 is localized in the endoplasmic reticulum and catalyzes both the 17-hydroxylation of pregnenolone and progesterone and the 17,20 bond scission of 17-hydroxypregnenolone and 17-hydroxyprogesterone. Because the hydroxylase activity is required for glucocorticoid production and both the hydroxylase and lyase activities are essential for adrenal androgen biosynthesis, the activities of this enzyme are positioned to direct hormone identity and adrenal output.

2. Signaling Pathways

Steroidogenic capacity is governed by peptide hormones that are secreted by the anterior pituitary in response to signaling from the hypothalamus. These peptide molecules evoke changes in steroid hormone output by acting as ligands for G protein-coupled receptors. Although numerous signaling molecules have been implicated as regulators of steroidogenic gene transcription in the adrenal cortex,[1] the most important factor in glucocorti-

coid production and *CYP17* regulation is ACTH.[2–7] This peptide hormone promotes steroidogenesis by activating intracellular signaling pathways that facilitate cholesterol uptake, transport, and delivery,[8,9] and induce steroidogenic gene transcription.[2,10–14] The trophic actions of ACTH are multi-faceted and allow for rapid production of steroid hormones by increasing substrate availability and sustained biosynthetic capacity by inducing gene expression.

Perhaps the most widely studied pathway is the cAMP signaling cascade. ACTH binding to the melanocortin 2 receptor results in the activation of the adenylyl cyclase, increased intracellular cAMP and activation of the cAMP-dependent protein kinase (PKA). PKA then acts to phosphorylate downstream targets, such as CREM (cAMP response element modulator), which induces steroidogenic acute regulatory protein (StAR) transcription,[15] and hormone sensitive lipase,[16] for the production of free cholesterol. It is anticipated that future research will identify other proteins whose function in steroidogenesis is regulated by PKA-catalyzed phosphorylation.

We have shown that ACTH rapidly activates the synthesis and secretion of the bioactive sphingolipid sphingosine-1-phosphate (S1P).[17,18] S1P is then secreted into the extracellular space where it binds to members of the S1P family of GPCRs, ultimately resulting in CYP17 transcription and cortisol production.[17,18] Since we have recently identified another sphingolipid, sphingosine, as an endogenous antagonist of the nuclear receptor steroidogenic factor-1 (SF-1, NR5A1, Ad4BP),[19] it is probable that ACTH also increases the transactivation potential of SF-1 by promoting dissociation of sphingosine and rapid conversion to S1P. ACTH also rapidly and transiently activates salt-inducible kinase 1, which results in translocation of the enzyme from the nucleus to the cytoplasm where it represses the transcription of steroidogenic enzymes,[20–23] thereby providing a mechanism by which adrenocortical cells fine-tune the kinetics of hormone output.

Activation of growth factor signaling pathways such as the mitogen-activated kinase (MAPK) cascade modulates *CYP17* gene expression.[24–28] Both epidermal growth factor and basic fibroblast growth factor, probably by activating the MAPK pathway, suppress CYP17 mRNA expression in H295R cells.[26] Src kinase, another effector in growth factor signaling, modulates CYP17 mRNA expression and controls adrenal androgen biosynthesis in H295R cells.[29] The phorbol ester TPA (12-O-tetradecanoyl-phorbol-13 acetate), which activates protein kinase C, represses CYP17 mRNA expression in mouse adrenal.[28] Interestingly, recent studies have found that the thiazolidinedione and peroxisome proliferator activated receptor-γ (PPARγ) agonist pioglitazone suppresses the expression of CYP17 via a PPARγ-independent and MAPK-dependent mechanism in the H295R cell line.[30]

Another recently identified signaling mediator of aldosterone and cortisol production is the Wnt-signaling pathway.[31] Activation of the Wnt signaling pathway and transfection of a constitutively active β-catenin mutant in H295R cells both induced StAR reporter gene activity, adding to a rapidly expanding list of signaling molecules that modulate adrenocortical steroidogenesis.[31] Given that SF-1 synergizes with β-catenin in the activation of the rat inhibin alpha gene during adrenal development,[32] it is likely that Wnt-dependent signaling cascades will be found to play other critical roles in steroidogenesis, not only in the adrenal gland, but in other steroidogenic tissues as well. Additionally, the cloning and functional characterization of T-cell factor 4N has revealed that this transcription factor synergizes with β-catenin and SF-1 in transactivating target genes,[33] identifying another mechanism by which protein-protein interactions may modulate steroidogenic gene transcription.

Another emerging mechanism by which an extracellular signaling factor modulates *CYP17* gene expression is in the production of cortisol and dihydroepiandrosterone in the fetal adrenal, where placental corticotropin-releasing hormone (CRH) signaling induces the mRNA expression of several steroidogenic genes, including *CYP17*, and directly stimulates hormone secretion.[34,35] Interestingly, the stimulatory effects of CRH on cortisol production in human fetal adrenal cells were found to be additive with ACTH.[34]

3. Transcription Factors

Seminal work by the Miller and Waterman laboratories on the human and bovine *CYP17* promoters, established the role of trophic hormone-activated transcription in mediating increased steroid hormone output. The stimulatory actions of ACTH and cAMP on steroidogenic gene transcription were initially demonstrated using primary cultures of bovine adrenal cells.[36] Although an increase in mRNA expression supported a role for transcriptional activation in maintaining steroidogenic capacity, studies using nuclear-run on assays confirmed that gene transcription is a prerequisite for cortisol secretion.[37] Because binding of ACTH to the melanocortin 2 receptor activates adenylyl cyclase and increases intracellular cAMP, it was originally hypothesized that the cAMP response element binding protein (CREB) transcription factor mediated the induction of steroidogenic gene expression. However, unlike the rapid induction of transcription observed for other CREB targets such as the immediate early genes c-Fos and Jun-B,[38,39] the stimulatory actions of cAMP on steroidogenic gene expression was delayed and took hours when compared to cAMP-evoked changes in the expression of immediate early genes.[37,40] Moreover, in contrast to other CREB targets, increased steroid hydroxylase gene expression was cycloheximide-sensitive,[41] indicating the requirement for the translation of a protein(s) required for conferring ACTH/cAMP-dependent gene transcription. Indeed, subsequent studies by several groups led to

the identification of unique cAMP responsive sequences in the promoters of steroidogenic genes that were essential for expression in response to ACTH signaling.

For the human *CYP17* gene, cAMP-dependent transcription requires a region within the first approximately 65 base pairs upstream of the transcriptional initiation site.[42,43] ACTH/cAMP promote the assembly of a ternary complex containing SF-1, p54,[nrb] and polypyrimidine tract-binding-protein-associated splicing factor PSF.[43] Significantly, the affinity of this trimer for the human *CYP17* promoter is positively regulated by cAMP[43] and is sensitive to kinase and phosphatase activity.[44] SF-1 is a nuclear receptor that is essential for steroid hormone biosynthesis, endocrine development and function, and sex differentiation.[45–52] The ability of SF-1 to modulate gene expression and steroidogenesis is regulated by phosphorylation,[44,53–55] sumoylation,[56,57] acetylation,[58–60] and protein-protein interactions.[43,61–67] In addition to the roles of post-translational modification and protein-protein interaction, a role for ligand binding has emerged as integral in controlling receptor function.[19,68–72]

Recently, we have demonstrated that sphingosine (SPH)[19,73] and phosphatidic acid (PA)[70] are endogenous ligands for SF-1. Using mass spectrometry to analyze SF-1 that was isolated from the H295R human adrenocortical cell line, we identified SPH as an endogenous antagonist[19]. SPH is bound to SF-1 in unstimulated H295R cells and dissociates from the receptor in response to ACTH/cAMP stimulation. We determined that SPH inhibited the ability of SF-1 to activate *CYP17* gene transcription by promoting the binding of corepressor complexes to the receptor. Intriguingly, *in vitro* assays demonstrated that SF-1 can bind to several sphingolipids and phospholipids[19], indicating that the receptor has multiple ligands that are predicted to act in a cell-, tissue-, or developmental stage-specific manner to control target gene expression. To identify agonists for SF-1, we once again performed mass spectrometric analysis of the purified receptor and identified PA as the predominant phospholipid that bound to SF-1 in the human adrenal cortex. Unlike SPH, PA preferentially bound to the receptor in response to ACTH/cAMP stimulation and was an agonist. PA activated the transcription of *CYP17* and several other steroidogenic genes. Stimulation of the ACTH/cAMP signaling pathway increased nuclear PA concentrations by activating diacylglycerol kinase theta (DGKθ).[70] Interestingly, DGKθ binds to SF-1, indicating that ligand binding is facilitated by a direct interaction between the nuclear receptor and DGKθ. Based on these findings, we propose a mechanism by which SPH maintains low levels of steroid hormone production in the absence of ACTH/cAMP stimulation, and perhaps in response to growth factor stimulation, by keeping SF-1 in an inactive conformation, thereby stabilizing interactions between the receptor and corepressor proteins.[61] Upon ACTH/cAMP stimulation, SPH dissociates from the receptor and PA binds to the ligand

binding pocket, thus promoting the interaction with coactivator proteins such as steroid receptor coactivator-1 and the histone acetyltransferase GCN5 (general control nonderepressed 5), which we have shown to bind to the *CYP17* promoter in a complex with SF-1 in response to ACTH/cAMP signaling.[61]

In addition to the interaction of SF-1-containing complexes with the proximal promoter, the stimulatory protein (Sp) family of transcription factors also plays an integral role in modulating basal *CYP17* gene expression.[74,75] A complex containing Sp1, Sp3, and nuclear factor-1C bind to a second element distal to the SF-1 binding site.[74] Another transcription factor that regulates the expression of the human *CYP17* gene is sterol regulatory element binding protein 1c (SREBP1c).[17] SREBPs are transcription factors that not only function as cholesterol sensors,[76] but also regulate steroidogenic genes including *StAR*[77] and *CYP17*.[17] In response to the sphingolipid S1P, SREBP1c is cleaved and transported to the nucleus where it activates *CYP17* transcription.[17]

Another family of transcription factors that are key in maintaining steroidogenic gene expression in the human adrenal cortex is the GATA family of transcription factors. GATA transcription factors control gene expression, cell differentiation, and tumorigenesis in diverse cell types, including steroidogenic factories such as the gonads and adrenal gland.[78–82] A role for GATA-6 in regulating the transcription of *CYP17* in the H295R human adrenocortical cell line has been established, where synergy between GATA-6 and SF-1 directs adrenal androgen biosynthesis.[83] Interestingly, the expression of GATA-6 is positively regulated by cAMP,[84] suggesting a role for trophic hormone stimulation in fine-tuning the function of this transcription factor in steroidogenic tissues. The direct interaction of GATA-6 or GATA-4 and Sp1 mediates constitutive expression of *CYP17*.[75]

4. Summary

The studies discussed in this review highlight some of the research that has led to our current understanding of the mechanism underlying *CYP17* gene expression in the human adrenal cortex. It is expected that further studies will reveal more about the complex signaling pathways and transcriptional regulatory networks that maintain *CYP17* transcription and optimal cortisol output.

5. Abbreviations

ACTH, adrenocorticotropin; PKA, cAMP-dependent protein kinase; StAR, steroidogenic acute regulatory protein; MAPK, mitogen activated protein kinase; PPARγ, peroxisome proliferator-activated receptor γ; CREM, cAMP response element modulator; SF-1, steroidogenic

factor-1; CREB, cAMP response element binding protein; PA, phosphatidic acid; SPH, sphingosine; DGKθ, diacylglycerol kinase θ; CRH, corticotropin releasing hormone; SREBP1c, sterol regulatory element binding protein 1c

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Povzetek

Združevanje večih mehanizmov uravnavanja, kot so dostopnost substrata, encimska aktivnost in prepisovanje genov, zagotavlja optimalno količino steroidnih hormonov. V skorji nadledvične žleze pri človeku je optimalno izločanje glukokortikoidov zagotovljeno z delovanjem adrenokortikotropina (ACTH), ki izvaja transkripcijski pritisk na vse gene, vpletene v steroidogenezo. Eden od teh genov je *CYP17*, ki kodira P450c17α, ključni encim v proizvodnji kortizola in androgenov nadledvične žleze. Raven prepisovanja *CYP17* je uravnavana z mnogimi regulatornimi mehanizmi, ki se odzivajo na različne signale. Signalne poti so koordinirane na razvojni, vrstno- in tkivno-specifični ravni, z dodatno časovno/cirkadično ravnijo uravnavanja. Ta kratek pregled bo izpostavil ključne kaskade prenosa signala in opisal transkripcijske faktorje, za katere je znano, da vplivajo na izražanje gena *CYP17* v skorji nadledvične žleze.