Journal of Steroid Biochemistry & Molecular Biology 165 (2017) 18–37

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

Disorders in the initial steps of steroid hormone synthesis

Walter L. Miller*

Center for Reproductive Sciences, University of California, San Francisco, CA 94143-0556, United States

ARTICLE INFO

Article history:
Received 19 November 2015
Received in revised form 1 March 2016
Accepted 3 March 2016
Available online 6 March 2016

Keywords:
Cholesterol
CYP11A1
Lipoid CAH
Mitochondria
Niemann-Pick type C disease
StAR
Wolman disease

ABSTRACT

Steroidogenesis begins with cellular internalization of low-density lipoprotein particles and subsequent intracellular processing of cholesterol. Disorders in these steps include Adrenoleukodystrophy, Wolman Disease and its milder variant Cholesterol Ester Storage Disease, and Niemann-Pick Type C Disease, all of which may present with adrenal insufficiency. The means by which cholesterol is directed to steroidogenic mitochondria remains incompletely understood. Once cholesterol reaches the outer mitochondrial membrane, its delivery to the inner mitochondrial membrane is regulated by the steroidogenic acute regulatory protein (StAR). Severe StAR mutations cause classic congenital lipoid adrenal hyperplasia, characterized by lipid accumulation in the adrenal, adrenal insufficiency, and disordered sexual development in 46,XY individuals. The lipoid CAH phenotype, including spontaneous puberty in 46,XX females, is explained by a two-hit model. StAR mutations that retain partial function cause a milder, non-classic disease characterized by glucocorticoid deficiency, with lesser disorders of mineralocorticoid and sex steroid synthesis. Once inside the mitochondria, cholesterol is converted to pregnenolone by the cholesterol side-chain cleavage enzyme, P450scc, encoded by the *CYP11A1* gene. Rare patients with mutations of P450scc are clinically and hormonally indistinguishable from those with lipoid CAH, and may also present as milder non-classic disease. Patients with P450scc defects do not have the massive adrenal hyperplasia that characterizes lipoid CAH, but adrenal imaging may occasionally fail to distinguish these, necessitating DNA sequencing.

Contents

Abbreviations: ABC, ATP-binding casette; ACAT, acyl-CoA:cholesterol acyltransferase; ALLO, allopregnanolone; CAH, congenital adrenal hyperplasia; CESD, cholesterol ester storage disease; CoA, coenzyme A; CYP, cytochrome P450; DSD, Disordered sexual development; ER, endoplasmic reticulum; ERMES, endoplasmic reticulum-mitochondria encounter structure; FAD, flavin adenine dinucleotide; HDL, High density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl co-enzyme A; HPBCD, hydroxypropyl-β-cyclodextrin; IMM, inner mitochondrial membrane; INSIG, insulin-induced gene; LDL, low density lipoprotein; MAM, mitochondria-associated membrane; MENTHO, MLN64 N-terminal homologue; MLN64, metastatic lymph node clone 64; NAD(P)(H), nicotinamide adenine dinucleotide (phosphate) (reduced form); NPC, Nieman-Pick type C; NSF, *N*-ethylmaleimide sensitive factor; OSBP, oxysterol-binding protein; OMM, outer mitochondrial membrane; SF1, steroidogenic factor 1; SNAP, soluble NSF attachment protein; SNARE, soluble NSF attachment protein receptor; SR-B1, scavanger receptor B1; SREBP, sterol response element binding protein; StAR, steroidogenic acute regulatory protein; StarD, StAR-related lipid transfer domain; START, StAR-related lipid transfer; WD, Wolman disease.

* Correspondence to: Walter L. Miller, MD, Distinguished Professor of Pediatrics, Emeritus, Center for Reproductive Sciences, HSE1634 University of California, San Francisco San Francisco, CA 94143-0556, United States.
E-mail address: wlmlab@ucsf.edu (W.L. Miller).

http://dx.doi.org/10.1016/j.jsbmb.2016.03.009
0960-0760/

1. Intracellular cholesterol trafficking

1.1. Lipoproteins and cholesterol uptake

The pathways, genetics and enzymology of human steroidogenesis are reasonably well understood [1], but the mechanisms of intracellular cholesterol transport, especially in steroidogenic cells, are less well understood [2]. The human adrenal can synthesize cholesterol de novo, and several disorders of cholesterol biosynthesis have been described [3], but most of the cholesterol used in human steroid synthesis derives from uptake of plasma low-density lipoprotein (LDL) via receptor-mediated endocytosis [4], although cholesterol from high-density lipoproteins (HDL) may also contribute [5]. Most rodent steroidogenesis derives from HDL via scavenger receptor B1 (SR-B1), but this pathway plays a minor role in human steroidogenesis [6]. Concentrations of LDL cholesterol do not correlate with steroidogenesis, and children undergoing long-term treatment with parvastatin for familial hypercholesterolemia do not appear to have impairments of gonadal or adrenal steroidogenesis [7,8].

High concentrations of LDL will suppress 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis, encouraging receptor-mediated endocytosis of LDL [9]; the resulting endocytic vessicles fuse with lysosomes, where LDL cholesterol esters are hydrolyzed to free cholesterol by Lysosomal Acid Lipase (encoded by *LIPA* on chromosome 10q23.31). The resulting cholesterol may be re-esterified by acyl-CoA:cholesterol acyl transferase (ACAT, also known as sterol O-acetyltransferase, or SOAT1) and stored in lipid droplets, or it may be used for steroidogenesis [10]. Cholesterol may be liberated from stored cholesterol esters by Hormone-Sensitive Lipase, which is activated in response to ACTH. ACTH inhibits ACAT, but stimulates the activity of HMG-CoA reductase, LDL receptors, and uptake of LDL cholesterol, thus increasing the availability of free cholesterol for steroid hormone synthesis, whereas normal concentrations of LDL suppress HMG-CoA reductase. Cholesterol ester hydrolase and neutral cholesterol ester hydrolase can both hydrolyze cytosolic cholesterol esters, but their relative contributions are unclear [11]. LDL cholesterol esters enter the cell via receptor-mediated endocytosis to endosomes, and are then stored directly or converted to free cholesterol [4]. Cholesterol esters that enter the cell via SR-B1 are further modified by Hormone-Sensitive (neutral) Lipase (encoded by *LIPE* on chromosome 19q13.1-q13.2) [12]. Irrespective of its source, cholesterol is essentially insoluble in water (critical micellar concentration, ~25–40 nM) [13]. Thus intracellular cholesterol trafficking employs two mechanisms: 'vesicular transport', where membranes fuse with other membranes to deliver cholesterol from one compartment to another, or 'non-vesicular transport', which involves cholesterol-binding proteins [14]. In mice, both Hormone-Sensitive Lipase and microsomal neutral cholesterol ester hydrolase 1 (Nceh1) participate in cholesterol deesterification [15,16]. Steroidogenic cells prefer to use cholesterol derived from circulating lipoprotein particles, but endogenous production of cholesterol can suffice: patients with congenital abetalipoproteinemia have low LDL cholesterol but have normal basal cortisol concentrations and only mildly impaired ACTH-stimulated cortisol secretion, and patients treated with statins have normal cortisol secretion [7,8].

1.2. Intracellular cholesterol homeostasis and processing

The expression and activation of HMG-CoA reductase is regulated by the sterol regulatory element-binding proteins (SREBPs), which coordinate and regulate cellular uptake, transport, and utilization of cholesterol. These transcription factors regulate genes involved in lipid metabolism and adipocyte differentiation and share the basic helix–loop–helix–leucine zipper (bHLH-Zip) structure [17–20]. The large C-terminal domain aligns two closely spaced membrane-spanning helices in the endoplasmic reticulum (ER) in a hairpin configuration, so that the N-terminal domain containing the transcriptional activation and DNA-binding domains become juxtaposed with the C-terminal regulatory domain on the cytoplasmic side of the ER [19]. The C-terminal domain interacts with the SREBP-cleavage-activating protein (SCAP), and insulin-induced genes 1 and 2 (INSIGs), serving as a cellular cholesterol sensor. SCAP is an 8-transmembrane protein; its loop 1 projects into the lumen of the ER and contains the cholesterol-binding site, and loop 6 projects into the cytosol and interacts with coat protein II complex (COPII). Cholesterol binding to loop 1 of SCAP controls the conformation of loop 6, thereby controlling interactions with COPII and hence the transport of the active fragment of SREBP to the nucleus, determining whether cells produce cholesterol [21]. SREBP-SCAP dissociates from INSIGs when cholesterol concentrations fall below a certain level; subsequently two proteolytic SREBP cleavages in the Golgi apparatus release the ~50 kDa "mature" N-terminal fragment of SREBP. This molecule moves to the nucleus where it activates target gene transcription by binding to sterol-regulatory elements in the promoters of target genes, and ultimately increasing sterol accumulation by both increased synthesis and increased import [22,23]. The feedback mechanism follows the increase in ER cholesterol by stabilizing the INSIG-SCAP-SREBP2 complex within the ER and suppressing further SREBP2 activities. The presence of this complex in the cholesterol-poor ER serves as a cholesterol sensing mechanism that regulates the synthesis and non-