

Dehydroepiandrosterone Research: Past, Current, and Future

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Abstract

The discovery of "oestrus-producing" hormones was a major research breakthrough in biochemistry and pharmacology during the early part of the 20th century. The elucidation of the molecular weight and chemical structure of major oxidative metabolites of

dehydroepiandrosterone (DHEA) led to the award of the Nobel Prize in 1939 to Adolf Frederick Johann Butenandt and Leopold Ruzicka. Considered a bulk androgen in the circulation, DHEA and its sulfated metabolite DHEA-S can be taken up by most tissues where the sterols are metabolized to active androgenic and estrogenic compounds needed for growth and development. Butenandt's interactions with the German pharmaceutical company Schering led to production of gram quantities of these steroids and other chemically modified compounds of this class. Sharing chemical expertise allowed Butenandt's laboratory at the Kaiser Wilhelm Institute to isolate and synthesize many steroid compounds in the elucidation of the pathway leading from cholesterol to testosterone and estrogen derivatives. As a major pharmaceutical company worldwide, Schering AG sought these new biological sterols as pharmacological agents for endocrine-related diseases, and the European medical community tested these compounds in women for conditions such as postmenopausal depression, and in men for increasing muscle mass. Since it was noted that circulating DHEA-S levels decline as a function of age, experimental pathology experiments in animals were performed to determine how DHEA may protect against cancer, diabetes, aging, obesity, immune function, bone density, depression, adrenal insufficiency, inflammatory bowel disease, diminished sexual function/libido, AIDS/HIV, chronic obstructive pulmonary disease, coronary artery disease, chronic fatigue syndrome, and metabolic syndrome. While the mechanisms by which DHEA ameliorates these conditions in animal models have been elusive to define, even less is known about its role in human disease, other than as a precursor to other sterols, e.g., testosterone and estradiol. Our groups have shown that DHEA and many of its oxidative metabolites serve as a low-affinity ligands for hepatic nuclear receptors, such as the pregnane X receptor, the constitutive androstane receptor, and estrogen receptors α/β (ER α /ER β) as well as G protein-coupled ER (GPER1). This chapter highlights the founding research on DHEA from a historical perspective, provides an overview of DHEA biosynthesis and metabolism, briefly summarizes the early work on the beneficial effects attributed to DHEA in animals, and summarizes the human trials addressing the action of DHEA as a therapeutic agent. In general, most human studies involve weak correlations of circulating levels of DHEA and disease outcomes. Some support for DHEA as a therapeutic compound has been demonstrated for postmenopausal women, in vitro fertilization, and several autoimmune disorders, and adverse health effects, such as, acne, embryo virilization during pregnancy, and possible endocrine-dependent cancers.



1. DISCOVERY OF DEHYDROEPIANDROSTERONE AND ITS HORMONE METABOLITES

1.1 Nobel Prize for “Oestrus-Producing” Hormones

The discovery of the chemical composition of “oestrus-producing” hormones was a major research effort in biochemistry and pharmacology during the early part of the 20th century. The elucidation of the chemical structure,

design of chemical synthesis, and the concept of a metabolic pathway leading from cholesterol to biologically active metabolites of dehydroepiandrosterone (DHEA) led to the award of the Nobel Prize in 1939 to Adolf Frederick Johann Butenandt for discovery and characterization of the sterol character of “Oestrus-producing” hormones and to Leopold Ruzicka for developing the unique chemical synthesis for androsterone. Butenandt and his research group discovered androsterone (Butenandt, 1931), testosterone (Butenandt & Hanisch, 1935), progesterone (Butenandt & Westphal, 1934), and also codiscovered estrone (Butenandt, 1929) with Edward Adelbert Doisy. The competition between the Butenandt and Doisy laboratories is discussed in the timely review by Simpson and Santen (2015). Although not included as an awardee in the 1939 Prize, Doisy was later recognized for his work on chemistry of vitamin K, and he was awarded the Nobel Prize in Medicine in 1943 with Henrik Carl Peter Dam who first discovered vitamin K. Due to a policy of the German Government at that time, Butenandt was forced by the “Greater German Reich” to decline the award in 1939 in Stockholm, but in 1949, he received the Nobel diploma and award from the Nobel Foundation. Butenandt and Dannenberg (1940) reported the presence of DHEA in urine and named the compound Prasterone. In 1944, DHEA-sulfate (DHEA-S) was first isolated in blood (Munson, Gallagher, & Koch, 1944) and later, Etienne-Emile Baulieu found DHEA and DHEA-S are produced by adrenal secretion (Baulieu et al., 1965). The sulfated species can be taken up by most tissues and subsequently desulfated to yield DHEA that can be metabolized to active androgenic and estrogenic compounds within the cell (Yen, 2001).

1.2 Relationship Between the Kaiser Wilhelm Institute Für Biochemie and the Schering AG Company

An advantage that Butenandt had was his extensive interactions with the Schering AG pharmaceutical company in Berlin, the site for both Butenandt’s laboratory and Schering’s research and production facility. This is well documented in the historical study of this relationship described by Gaudilliere (2005). First, contracts with Schering AG provided additional funds beyond that provided by the Foundation that supported the Kaiser Wilhelm Institute für Biochemie, Berlin-Dahlem, Germany (KWIB). This allowed Butenandt to fill his laboratory with excellent young German chemists, supplies, and equipment for experiments. Second, Schering AG allowed his group access to their pilot plant for purification of sex hormones from isolates of starting materials, thereby facilitating the effort

of crystallization of steroids from human urine, blood, or tissues. This allowed Butenandt to have a large amount of natural starting materials for the crystallization process to obtain testosterone, progesterone, and dehydroandrosterone. In addition, as the Butenandt Laboratory crystallized new urinary or serum sterols and characterized them chemically, this information was shared with Schering AG that tested these lead compounds in biological assays (see [Section 1.3](#)). In addition, Schering AG chemists could begin devising chemical synthesis methods to obtain these compounds and their derivatives in bulk from cholesterol or bile acids. The availability of these chemical standards was in turn valued by Butenandt as he began to dissect the steroid biosynthetic pathway. This result can best be seen from his efforts to form dehydroandrosterone (what is now known as DHEA) from cholesterol. From this work, he proposed that males and females use the same biosynthetic pathway to form compounds with male or female gonad-specific properties predicted from his detailed biochemical pathway for androgen and estrogen production published in 1936 ([Butenandt, 1936](#)).

Since both Butenandt and Schering AG believed that these natural steroid hormones would be important pharmaceutical agents, they copatented many of these compounds in the 1930–1940s. This interesting Academic–Industry relationship was highly beneficial to the advancement of biochemical understanding of steroid hormones and provided important lead compounds to Schering AG that were promising new pharmaceuticals. Most of the early compounds isolated by the Butenandt laboratory were produced by collecting urine from humans or horses or from sow ovary and the isolation of natural products required concentrating the sterols many 1000-fold prior to crystallizing them. The large scale-up procedure required for isolating natural sterols often did not provide enough of the isolated steroid for industrial production. Therefore, Schering AG turned to chemical synthesis utilizing the processes published by Leopold Riczika, the coawardee for the 1939 Nobel Prize. Riczika, a Professor of Organic Chemistry at University of Utrecht, and later from the Eidgenössische Technische Hochschule in Zürich, developed a unique synthesis of these sterols from cholesterol.

1.3 The Early Studies in the Physiological Role of “Oestrus-Producing” Hormones to Identify Active Steroid Hormones

The isolation of these biologically active sterols required a biological endpoint to demonstrate whether they had any physiological function. A number of animal-based assays were developed, some performed at the KWIB and others at Schering AG or other contract companies associated

with Schering AG. At that time, there were three major pharmaceutical companies interested in exploiting this emerging understanding of active sterols, namely, Schering at Berlin-Dahlem, Organon in Amsterdam, and Chemische Industrie Basel (CIBA) in Basel. All decided that there was a significant market for the sex steroids and set about to have their own facilities built to extract hormone from urine or organs for the market. Hoffman-La Roche and CIBA both devoted attention to unique synthesis of these steroids, leading to their support of Leopold Ruzicka's chemical synthesis efforts ([Gaudilliere, 2005](#)).

A number of assays were rapidly developed to test biological action of these newly identified sterols. The Allen–Doisy mouse test ([Allen & Doisy, 1983](#)) allowed researchers to inject various estrogens or other gonadal steroids into ovariectomized rodents and test whether they noted increased cornification of epithelial cells in vaginal smears or disappearance of leukocytes as a proof of estrogenic activity. Budenandt's group measured for androgen action by measuring the growth of the crest in castrated chickens after injection of androsterone and other steroids they isolated or synthesized. Similar animal-based assays that measured a known estrogen- or androgen-dependent phenotype were used in all of the pharmaceutical companies and laboratories. The Animal Facilities developed at Schering AG and other companies became independent research facilities as they improved techniques in these bioassays. This initially allowed sharing of reagents and expertise between the KWIB and Schering AG that diminished as Schering AG moved toward independence from its association with KWIB scientists. Eventually at the end of the World War II, Butenandt moved his research group to Tübingen in anticipation of the Russian invasion of eastern Germany. As described by [Gaudilliere \(2005\)](#), the close reliance between research institutes and industry was lost at the end of the war and Butenandt changed fields looking at insect pheromones and other natural products. The pheromone Bombykol (ironically, a steroid) was isolated from female silkworms and characterized by Butenandt in 1961 ([Butenandt, Beckmann, & Stamm, 1961](#)).

Although Butenandt had views of how these steroids could be used in medicine, Schering AG had its own collection of affiliated physicians who were applying these compounds in clinics in Germany ([Gaudilliere, 2005](#)). One example of medical experimentation was seen in the collaboration between Schering AG with two clinical research groups, namely, C. Kaufman's Frauenklinik der Charité in Berlin and Carl Clauberg at the gynecological clinic at Königsberg University. Kaufman published the use

of Progynon (estriol glucuronide and estriol sulfate from women's urine) and Proluton (hydroxyprogesterone caproate) for the treatment of infertile women (Kaufmann, 1934). These compounds induced menses in women. Kaufmann apparently advocated these compounds as a way to manage many of the symptoms of postmenopausal women (Gaudilliere, 2005). Clauberg utilized these compounds in laboratory-based research to develop better biological assays for progesterone. Some of his work addressed control of fertility, heralding future work for the use of steroids in preventing conception (Clauberg, 1935). This work, described by Gaudilliere (2005), was the beginning of an expansion of medical use of these steroid hormones in medicine. In fact, Gaudilliere describes that Schering AG in 1945 constructed a new plant at the end of World War II to increase production of *Progynon*, *Proluton*, and *Testoviron* (Gaudilliere, 2005).

In preparing this chapter, we posited whether these early clinical studies demonstrating some beneficial effects upon administration of such hormonal preparations lead to the continued study of DHEA for the next 40 years. However, what was not known at that time was the normal functioning of the hormonal system in men and women and the ability of a single biosynthetic pathway to provide differential steroid levels to regulate expression of gender. With the initial successes in the clinic to benefit conditions, e.g., regulation of the menstrual cycle, infertility, and pregnancy, physicians throughout the world continued their "clinical" investigations with industry-produced steroids for medicine as part of their regular medical practice.



2. DHEA SYNTHESIS AND METABOLISM

2.1 DHEA Synthesis in the Adrenal *Zona Reticularis*

With the discovery of high concentrations of circulating DHEA-S in human blood, considerable interest arose to understand where and how DHEA and its sulfated form are produced. In an elegant study, Baulieu et al. (1965) discovered DHEA and DHEA-S are synthesized in the adrenal and thus began our understanding of the biochemical pathway. In the same year, MacDonald and Siteri demonstrated that estrogen production in pregnant women is derived from circulating DHEA (MacDonald & Siteri, 1965). In addition, MacDonald and coworkers developed isotope dilution methods to study the conversion of DHEA to various hormones in humans which subsequently allowed definition of how estrogen, testosterone, and dihydrotestosterone (DHT) are synthesized (Deshpande & Bulbrook, 1964; Gurpide,

MacDonald, Chapdelaine, Vande Wiele, & Lieberman, 1965). Many studies on the enzymatic processes for the production of estrogen, testosterone, and DHT from androgens, such as DHEA/DHEA-S, pursued. These metabolic pathways are briefly summarized later.

It is well established that DHEA is synthesized *de novo* from cholesterol mainly in the adrenal, ovary, and testis. In addition, there is limited production of DHEA in cells of the cerebral cortex and other cell types in the brain (Rossetti, Cambiasso, Holschbach, & Cabrera, 2016; Zwain & Yen, 1999). However, it is recognized that adrenal production accounts for the majority of the circulating levels of DHEA and DHEA-S. The adult adrenal cortex has three distinct zones characterized by specific gene expression patterns that lead to specific steroid output (reviewed in Turcu, Smith, Auchus, & Rainey, 2014). The *zona glomerulosa* (ZG), *fasciculata* (ZF), and *reticularis* (ZR) are the sites for mineralocorticoid (aldosterone), glucocorticoid (cortisol), and androgen (DHEA/DHEA-S) synthesis, respectively. The gonads are the major site for sex hormone production, and, in the testis and ovary, DHEA serves as an intermediate steroid within the testosterone and estradiol biosynthetic pathways, respectively. Peripheral tissues that uptake DHEA/DHEA-S from circulation typically generate more potent androgens and estrogens that act locally. In healthy adult males, less than 5% of the total circulating testosterone (T) levels is from peripheral metabolism of DHEA. However, under conditions of loss of testicular T production, DHT levels in the prostate are maintained by DHEA metabolism (Labrie et al., 2005). In healthy women, peripheral metabolism of DHEA is a major contributor to circulating sex hormone levels with 40%–75% of T in premenopausal women and over 90% of the estrogens in postmenopausal women derived from adrenal androgens.

The DHEA biosynthetic pathway in the adrenal *zona reticularis* is shown in Fig. 1. The first regulated step is the transfer of cholesterol across the mitochondrial membranes to the cytochrome P450 (CYP) side chain cleavage enzyme (CYP11A1 encoded by the *CYP11A1* gene). CYP11A1 is anchored in the inner membrane by an amino-terminal α -helix with the catalytic site oriented toward the matrix. The movement of cholesterol from the mitochondrial outer membrane to the CYP11A1 catalytic site is dependent on the action of the steroidogenic acute regulatory protein (STAR, *STARD1*) (Stocco, Zhao, Tu, Morohaku, & Selvaraj, 2017). CYP11A1 cleaves the side chain of cholesterol-producing pregnenolone using electrons from NADPH that are shuttled to the enzyme via FAD-containing adrenodoxin reductase and an iron-sulfur protein, adrenodoxin

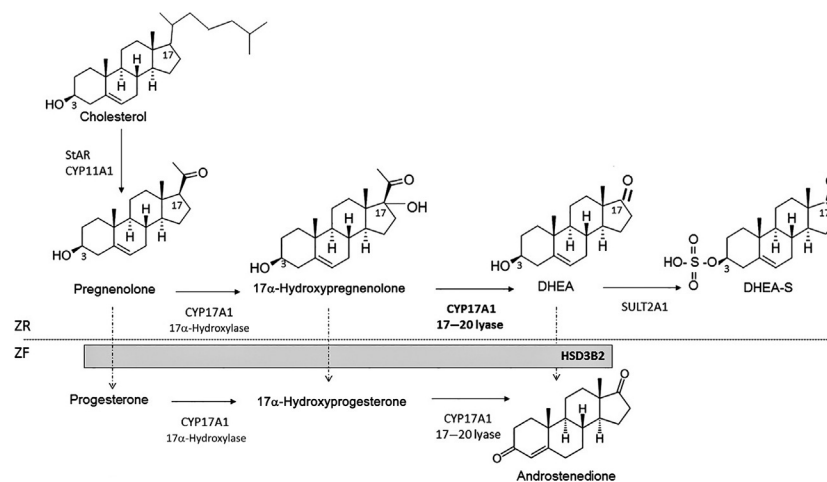


Fig. 1 DHEA biosynthetic pathway. DHEA/DHEA-S in circulation mainly originates from the adrenal. Shown are the key enzymes and steroid intermediates in the adrenal *zona reticularis* (ZR) and *zona fasciculata* (ZF). The pathway and enzyme activities are described in the text. *StAR*, steroidogenic acute regulatory protein; *CYP11A1*, cytochrome P450 side-chain cleavage; *CYP17A1*, cytochrome P450 17α-hydroxylase, 17,20 lyase (one enzyme, two activities); *HSD3B2*, 3β-hydroxysteroid dehydrogenase; *SULT2A1*, sulfotransferase family 2A member 1.

(Mast et al., 2011). Pregnenolone produced in the mitochondria moves to the endoplasmic reticulum and to the catalytic site of cytochrome P450 17α-hydroxylase/17,20 lyase (CYP17A1 encoded by the *CYP17A1* gene) (reviewed in Auchus & Rainey, 2004). CYP17A1 is a type 1 integral membrane protein that has two distinct catalytic actions hydroxylation at C17 of the steroid nucleus forming 17α-hydroxypregnenolone, and hydrolysis of the C17–C20 bond of 17α-hydroxypregnenolone to generate DHEA. Again, this P450-dependent reaction requires electrons from NADPH, and for endoplasmic reticulum-resident P450s the cytochrome P450 oxidoreductase (encoded by the *POR* gene) that contains both FMN and FAD centers to shuttle electrons from NADPH to CYP17A1 (reviewed in Miller, 2005). These reactions generate a keto group at C17, which, along with the C3-β-hydroxyl group and a double bond between C5 and C6 of the B ring in the steroid nucleus, provides the unique sterol structure for DHEA: 5-androsten-3β-ol-17-one (Fig. 1).

As stated previously, the major circulating form of DHEA is DHEA-S. DHEA sulfonation in the adrenal is catalyzed by sulfotransferase family 2A member 1 (SULT2A1) that conjugates sulfuryl (SO₃) to the C3-β-hydroxyl

group of DHEA-producing DHEA-S (Wang, Cook, Falany, & Leyh, 2014). Three biochemical consequences of DHEA sulfonation are (1) DHEA-S has higher binding affinity for albumin and a 50-fold longer half-life in circulation compared to DHEA (Longcope, 1996); (2) DHEA-S uptake by a cell requires active transport by a member of the solute carrier organic anion transporter family (Mueller, Gilligan, Idkowiak, Arlt, & Foster, 2015); and (3) DHEA-S is classified as biologically inactive, e.g., unable to bind receptor(s), although this classification is being challenged by new studies (see chapter by Clark, Prough, & Klinge, 2017, in this volume).

2.2 Peripheral DHEA Metabolism

Generally, DHEA-S action is dependent upon cellular uptake and conversion back to DHEA. Members of the solute carrier organic anion transporter family that are capable of transporting sulfated steroids include solute organic anion transport (SOAT encoded by SLC10A6) and organic anion transporter polypeptide-1A2 (OATP-1A2 encoded by SLCO1A2). SOAT is predominant in adipose and placenta, while OATP-1A2 is high in brain, liver, and kidney. Steroid sulfatase (encoded by the *STS* gene) is a ubiquitously expressed enzyme that hydrolyzes the sulfonyl group from DHEA-S to produce DHEA. Thus, a cell that expresses an STS is capable of using DHEA-S to generate DHEA which may be further metabolized to sex hormones in a cell type-dependent manner (reviewed in Mueller et al., 2015) (Fig. 2). This intracellular control of androgen and estrogen levels and the subsequent biological response within the cell is defined as an intracrine mechanism of action (reviewed in Labrie, Martel, Belanger, & Pelletier, 2017). The major tissues associated with DHEA-S metabolism are placenta, ovary, testes, prostate, adipose, liver, and brain—tissues associated with sex hormone-nuclear receptor-driven processes.

DHEA serves as the precursor for the weak androgens, androstenedione (4-androstene-3 β ,17 β -dione, Adione) and androstenediol (5-androstene-3 β ,17 β -diol, Adiol). To generate Adione the 3 β -hydroxy group of DHEA is oxidized to a keto group along with isomerization of the double bond from C6–C5 in the B ring to C5–C4 in the A ring of the steroid nucleus. DHEA, DHEA-S, and Adione are commonly referred to as C17 keto steroids and represent the major adrenal androgens in circulation (Figs. 1 and 2). Adiol is generated by reduction of the C17 keto group to a 17 β -hydroxyl group and is a relatively minor adrenal androgen (Fig. 1). Adione and Adiol both serve as precursors for testosterone and estradiol synthesis, thereby

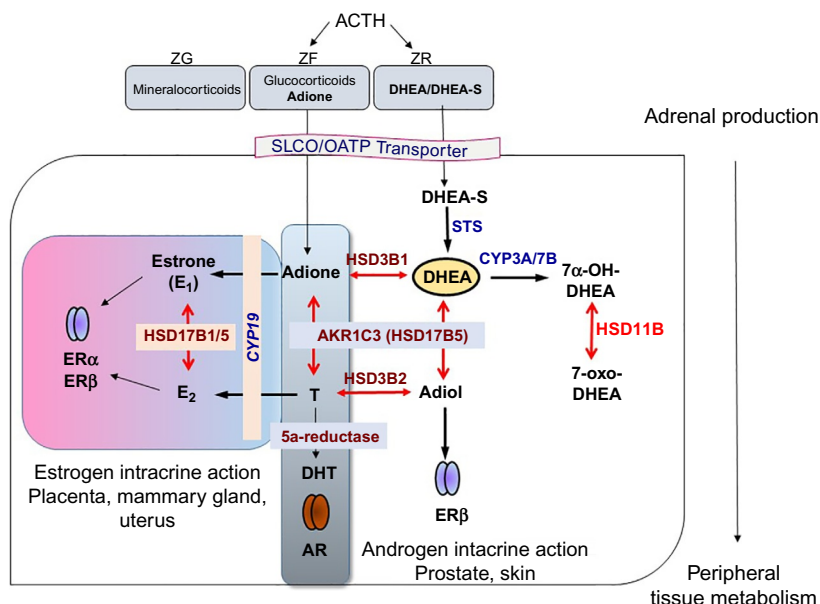


Fig. 2 Peripheral metabolism of adrenal androgens. This schematic depicts the metabolism of the major circulating adrenal-derived weak androgens, DHEA-S, DHEA, and androstenedione (Adione). The pathways and enzyme activities are described in the text. Cellular uptake of DHEA-S and Adione is mediated by members of the solute carrier organic anion transporter family (SLCO) and the organic anion transporter polypeptide family (OATP). DHEA-S is desulfated by steroid sulfatase (STS) prior to further metabolism. The conversion of DHEA and Adione to estrogens (estradiol and estrone) and/or testosterone is dependent upon the relative expression in a particular cell/tissue of the enzymes shown. DHEA metabolism to estrogens in estrogen responsive tissues and the sex hormone acts locally by binding estrogen receptor-alpha and/or estrogen receptor-beta ($ER\alpha$ and $ER\beta$). DHEA metabolism to potent androgens testosterone (T) and dihydrotestosterone (DHT) occurs in androgen-responsive tissues and the sex hormones act locally by binding the androgen receptor (AR). ERs and AR are members of a family of nuclear receptors that bind as a homodimer to DNA and either activate or inhibit gene transcription. DHEA metabolism to 7 α -hydroxy-DHEA and 7-oxo-DHEA occurs in the liver via the actions of cytochrome P450 3A (CYP3A) or 7B (CYP7B) and 11 β -hydroxysteroid dehydrogenase (HSD11B), respectively. *Adiol*, 5-androsten-3 β ,17 β -diol; *Adione*, 4-androstene-3 β ,17 β -dione; *HSD3B*, 3 β -hydroxysteroid dehydrogenase; *HSD17B*, 17 β -hydroxysteroid dehydrogenase. HSD17B1/3/5 are different isoforms with tissue, substrate, and activity specificity.

providing the route for adrenal-derived DHEA/DHEA-S contribution to sex hormone action in peripheral tissues (Fig. 2). The adrenal is capable of metabolizing DHEA to androstenedione (Adione) and androstenediol (Adiol) that serve as precursors for the sex hormones testosterone (T) and

estrogens (E1 and E2) (Fig. 1), yet this represents a very minor pathway for contribution to circulating steroid levels.

Members of the Short Chain Dehydrogenase family are responsible for DHEA, Adione, and Adiol metabolism. 3β -Hydroxysteroid dehydrogenase/ Δ^5 - Δ^4 isomerase (HSD3B) catalyzes the irreversible isomerization reaction that changes Δ^5 steroids (defined as containing a C6–C5 double bond in the steroid B ring) to Δ^4 steroids (defined as steroids containing a C5–C4 double bond in the steroid A ring) that include DHEA to Adione, and Adiol to T (Figs. 1 and 2). In the adrenal and gonads, HSD3B type 2 (HSD3B2) is the major isoform expressed. However, the adrenal *zona reticularis* has high CYP17A1-17,20 lyase activity, high SULT2A1 expression, and low HSD3B2 activity that drives the pathway toward DHEA/DHEA-S (Fig. 1). Higher HSD3B2 activity in the other adrenal zones favors mineralocorticoid and glucocorticoid synthesis from pregnenolone and 17α -hydroxypregnenolone, respectively. HSD3B type 1 (HSD3B1) is the major isoform expressed in steroid responsive tissues including placenta, prostate, and skin and is a key for intracrine action of DHEA by converting DHEA to Adione, and Adiol to T (Fig. 2). Importantly, 17β -hydroxysteroid dehydrogenase (HSD17B) family members catalyze reversible oxidation–reduction at C17 to interconvert between steroids containing either C17 keto or C17 hydroxyl groups. HSD17B isoforms type 1 and 3 preferentially catalyze the reduction of a C17 keto group to a β -hydroxyl group for generation of the potent sex hormones T and estradiol (E2) that are characterized by a C17 β -hydroxyl group. HSD17B3 is highly expressed in the testis for T production, while HSD17B1 is the isoform expressed placenta, ovary, and mammary gland with substrate specificity for estrogens over androgens. In the adrenal, C17 keto reduction is catalyzed by a member of the aldo–keto reductase family, AKR1C3 (alias HSD17B5) (Fig. 1). AKR1C3/HSD17B5 also is the major isoform that catalyzes the peripheral metabolism of DHEA to Adiol, Adione to T, and estrone to E2 (Fig. 2). Adione and T are substrates for the enzyme 5α -reductase (encoded by the *SRD5A2* gene) that reduces the double bond in the A ring to form 5α -Adione and DHT, respectively (Fig. 2). DHT is reported to have higher affinity binding to the nuclear steroid receptor, androgen receptor (AR), and increases AR stability relative to T binding, thereby making DHT the most potent androgen for AR activation (Zhou, Lane, Kempainen, French, & Wilson, 1995). 5α -Reductase is highly expressed in prostate, seminal vesicles, hair follicles, and skin where intracrine actions of DHT promote AR-dependent signaling for growth and development.

Further, androgens are converted to estrogens by the action of aromatase (CYP19A1) that catalyzes a complex series of reactions that result in aromatization of the A ring and demethylation at C19. Aromatase converts Adione and T to estrone and estradiol, respectively (Fig. 2). Lastly, cytochrome P450-dependent metabolism (CYP) of DHEA generates monohydroxylated DHEA metabolites with 7 α -hydroxy-DHEA shown to be further metabolized to 7-oxo-DHEA by 11 β -hydroxysteroid dehydrogenase (HSD11B) (Fitzpatrick, Ripp, Smith, Pierce Jr, & Prough, 2001; Hennebert et al., 2009; Robinson, Michael, Ripp, Winters, & Prough, 2003) (Fig. 2).

The importance of peripheral DHEA metabolism increases in disorders in gonadal steroid production and with age and declining gonadal function (Lois, Kassi, Prokopiou, & Chrousos, 2000). Conversely, polycystic ovarian disease (PCOS) and nonclassical 21-hydroxylase-deficient congenital adrenal hyperplasia (Goodarzi, Carmina, & Azziz, 2015) are disorders associated with elevated DHEA-S and T of adrenal origin. In these patients, the elevated DHEA may contribute to symptoms of PCOS disease by direct receptor activation and not simply supplying precursor steroid for T production (Daan et al., 2015; Moran, Arriaga, Arechavaleta-Velasco, & Moran, 2015; Pinola et al., 2015). To date, hormone-dependent cancers provide the best examples for possible detrimental intracrine actions of sex hormone synthesis from DHEA/DHEA-S (Chang, Ercole, & Sharifi, 2014; McNamara & Sasano, 2015). In addition, adipose tissue is being increasingly recognized as an important player in peripheral metabolism of adrenal-derived DHEA/DHEA-S. The intracrine effects of adipose androgen production from DHEA/DHEA-S may regulate adipocyte differentiation and energy metabolism (Fujioka et al., 2012; O'Reilly, House, & Tomlinson, 2014). The contribution of adipose tissue to hormone imbalance disorders is an area that requires further investigation, especially given the rise in obesity.

2.3 Regulation of DHEA Synthesis and Metabolism

The developmental pattern for DHEA/DHEA-S synthesis is cyclical with the fetal adrenal producing high levels (providing the steroid precursor for placental estrogen synthesis) that fall to nadir levels after birth and remain low for the first 6 years of life. Elevations in serum DHEA/DHEA-S are coincident with the expansion and differentiation of the adrenal *zona reticularis*, a change that begins typically around 6–8 years of age and defines adrenarche (Auchus & Rainey, 2004; Rege et al., 2016). DHEA/DHEA-S

levels continue to rise and peak between the second and third decade of life. In healthy young adults, the circulating DHEA-S:DHEA ratio is 1000:1 with standard values ranging from 1 to 10 μ M DHEA-S compared to 2 to 30 nM for DHEA (Andus et al., 2003; Mueller et al., 2015) with women typically having lower levels than men. With age these levels decline and are 10-fold lower by 60–80 years of age (Labrie, 2010a; Labrie, Belanger, Cusan, Gomez, & Candas, 1997; Labrie et al., 2005). The association between age-related health disorders and the decline in DHEA sparked interest in the potential for restoring DHEA/DHEA-S levels as a “fountain of youth” treatment for aging-associated disorders (Baulieu, 1996). In 1994, Congress passed the Dietary Supplement Health and Education Act that opened the door for DHEA to be sold as an over-the-counter nutritional supplement (outside of the FDA’s jurisdiction), and DHEA was/is marketed as a therapeutic agent to promote many health benefits. However, the use of DHEA as a nutritional supplement is hotly debated since a causal relationship between DHEA levels and health benefits has not been clearly established despite four decades of research, and the potential for DHEA to increase sex hormone-driven cancer risk via local metabolism to sex hormones within the tumor elicits a cautionary note. The chapter by Clark et al. (2017, in this volume) focuses on the mechanism(s) for DHEA (and DHEA metabolites) action that are beginning to provide rationales for both the potential health benefits of this steroid and potential detrimental tumor-promoting actions.

Adrenocorticotropin hormone (ACTH) is capable of stimulating DHEA synthesis, as observed by increased circulating DHEA levels following ACTH stimulus in rodent and human studies. Further, DHEA levels follow a circadian pattern that parallels ACTH with levels of both hormones peaking in the morning (Hammer et al., 2005). ACTH binds to melanocortin-2 receptors (MC2R) expressed in the *zona fasciculata* and *reticularis* and activates cAMP-dependent protein kinase A (PKA)-dependent signaling. PKA signaling results in phosphorylation of key transcription factors such as SF-1, CREB/CREM, GATA4/6, and AP1 family members that activate *STAR*, *CYP11A1*, *CYP17A1*, and *SULT2A1* gene expression to maintain an increase in steroid output (Jimenez, Saner, Mayhew, & Rainey, 2003; Ruggiero & Lalli, 2016). Thus, the molecular mechanisms that control *StAR*, *CYP11A1*, *CYP17A1*, and *SULT2A1* expression in the adrenal ZR would be predicted to control DHEA/DHEA-S synthesis (Udhane & Fluck, 2016).



3. BENEFICIAL EFFECTS OF DHEA SUPPLEMENTATION

3.1 Early Studies That Sparked Research on DHEA Supplementation

Early studies in humans documented the levels of DHEA and DHEA-S in many disease states (Barrett-Connor, Khaw, & Yen, 1986; Bird, Masters, & Clark, 1984; Bulbrook & Hayward, 1965). For example, Bulbrook and Hayward (1965) and Bulbrook, Hayward, and Spicer (1971) reported that patients with breast cancer who excreted lower quantities of urinary 11-deoxy 17-oxosteroids relative to the 17-hydroxycorticosteroids have higher rates of breast cancer recurrence after mastectomy. Further, women who excrete lower levels of these androgens, now known to largely be DHEA-S, are at greater risk for breast cancer than women with higher levels of excretion (Bulbrook et al., 1971). These findings suggested lower DHEA excretion in urine (i.e., lower levels of circulating 17-hydroxycorticosteroids/urine) could be a predictive tool for breast cancer occurrence.

3.2 Summary of Effects of DHEA in Animal Models

A possible correlation between circulating DHEA-S levels and cancer risk encouraged further studies on DHEA's role in additional health issues and stimulated animal studies to address the mechanism of action of DHEA in these models. Kalimi and Regelson (1990, 2000) have coauthored two books on DHEA and wrote a review (Gursoy, Hu, Cardounel, Regelson, & Kalimi, 2011) that extensively covers DHEA beneficial effects in animal models. For the sake of brevity, we provide a summary of the animal work in table form (Table 1). We apologize to the many authors we have not cited, but the voluminous literature on DHEA effects on animal models prevent full review.

As an example of the breadth of these studies, the Schwartz research group at Temple University has examined on the role of DHEA administration on the management of cancer, obesity (Schwartz & Cleary, 1987), cancer chemoprotection (Pashko & Schwartz, 1983), and brain injury (Malik et al., 2003). This chapter will focus mainly on the human clinical trials.

3.3 Inhibition of Glucose 6-Phosphate Dehydrogenase by DHEA and Other Sterols

DHEA and other steroids have long been known to be potent inhibitors of glucose 6-phosphate dehydrogenase (G6PD), leading to decrease in both

Table 1 Beneficial Effects of DHEA Supplementation in Animal Models of Disease

Disease State	Animal Model	Conclusion on DHEA Action	References
Obesity	Rat (diet vs diet plus DHEA)	Weight gain decreased relative to control	Prough, Webb, Wu, Lapenson, and Waxman (1994), Schwartz and Cleary (1987), and Wu et al. (1989)
Chemoprevention of carcinogenesis	MNU breast cancer	Inhibition of tumor formation	Lubet et al. (1998)
	TPA-promoted skin cancer	DMBA DNA binding decreased	Pashko and Schwartz (1983)
Immune function	IL2 regulation in mouse	Enhanced immunity in mice	Araneo, Woods, and Daynes (1993) and Daynes, Dudley, and Araneo (1990)
Diabetes	Diabetes in rats	Reversed insulin insufficiency	Coleman, Leiter, and Schwizer (1982)
Atherosclerosis	Cholesterol ester accumulation	Reduced cholesterol in murine macrophages	Taniguchi, Yanase, Kobayashi, Takayanagi, and Nawata (1996)
		Reduced atherosclerosis in rabbits	Gordon, Bush, and Weisman (1988)

NADPH levels for reduction reactions and ribose phosphate levels for nucleotide synthesis (Menzel, Gobbert, & Oertel, 1970; Shantz, Talalay, & Gordon, 1989). G6PD inhibition may account for the cytostatic properties of DHEA. This theory was supported by studies showing that administration of ribose phosphate derivatives to female Wistar rats reduced the ability of dietary DHEA to inhibit liver tumor growth in vivo (Garcea et al., 1988). The G6PD inhibitory effect of DHEA, or other sterols with higher affinity to G6PD, involved reduced production of NADPH and ribose phosphates and remains an interesting chemoprotective mechanism that might be exploited to hinder tumor cell growth (Hamilton et al., 2012; Shantz et al., 1989).



4. BENEFICIAL EFFECTS OF DHEA SUPPLEMENTATION ON HUMAN DISEASE

After many reports on the positive effects of DHEA and DHEA-S supplementation on various animal models of disease (Table 1), a logical next question to address is whether the positive effects observed in animals could be recapitulated in humans and were there any negative side effects of DHEA supplementation? Table 2 lists the DHEA supplementation studies in aging humans demonstrating beneficial effects on symptoms of systemic lupus erythematosus (SLE) (Van Vollenhoven & McGuire, 1996), depression (Wolkowitz et al., 1997), AIDS (Centurelli & Abate, 1997), ulcerative colitis (Andus et al., 2003), vaginal atrophy (Labrie, 2010a, 2010b), diminished ovarian reserve (Fouany & Sharara, 2013; Nagels et al., 2015), and mood (do Vale et al., 2015), as well as its use as an adjuvant during immunization against tetanus and influenza (Evans et al., 1996). DHEA supplementation has also been associated with small decreases in adipose stores (Corona et al., 2013), a site for intracrine action of DHEA. This section will first summarize studies conducted by Baulieu and coworkers on DHEA supplementation effects on bone density (Baulieu et al., 2000), pulmonary hypertension and COPD (Debonneuil, Quillard, & Baulieu, 2006; Dumas de La Roque et al., 2012), and mental and physical aging (Baulieu, 1996; Mazat et al., 2001). Other selected areas covered include DHEA effects in female fertility and cardiovascular health.

4.1 Protocol DHEAge

“Protocol DHEAge” was a large (280 subjects) randomized, double-blind, placebo-controlled clinical trial. DHEA was administered either at a dosage of 50 mg daily or a placebo (per os) for a year (Baulieu et al., 2000). No harmful side effects due to DHEA administration were observed at 1 year, and, in addition to the expected increase in DHEA/DHEA-S levels in blood, modest increases in estrogens and testosterone were observed. DEXA scans revealed that bone density improved in women, and decreased osteoclastic activity was observed in subjects >70 years of age. Increases in libido in women >70 years of age were observed as well as improvement of skin texture. However, given the known role of estrogens and androgens in human breast and prostate cancer, it was deemed “medically justified to keep aging subjects who take DHEA ≤ 50 mg/day under appropriate clinical and biological control at reasonable time intervals.” We note that this paper has

Table 2 Beneficial Effects of DHEA Supplementation in Human Disease Confirmed

Disease State	Parameter Measured	Conclusion on DHEA Action	References
Pulmonary hypertension	6-Min walk test	Improved	Dessouroux, Akwa, and Baulieu (2008) and Dumas de La Roque et al. (2012)
	Carbon monoxide diffusing capacity of the lung (DLCO % predicted) increased significantly	Improved	
	Pulmonary hemodynamics	Improved	
Systemic lupus erythematosus	Lupus flares	Improvement	Van Vollenhoven and McGuire (1996)
Crohn's disease	Crohn's active index	Decreased	Andus et al. (2003)
	Ulcerative colitis	Decreased	
Vaginal atrophy	Hormone deficiency of menopause	Improved by local application	Labrie (2010a, 2010b)
	Sexual dysfunction	Improvement	
Infertility	Ovarian reserve	Improvement for fertility	Fouany and Sharara (2013) and Nagels, Rishworth, Siristatidis, and Kroon (2015)
Obesity	Body weight decline	Slight improvement in males only	Corona et al. (2013) and Morales, Haubrich, Hwang, Asakura, and Yen (1998)
Immune function	Response to immunization	Improvement	Evans et al. (1996)
	AIDs suppression	Improvement	Centurelli and Abate (1997)
Mood	Depression	Improvement	do Vale et al. (2015) and Wolkowitz et al. (1997)

been cited in 45 other papers in PubMed, including a meta-analysis that refuted the findings of the Baulieu study noting “low confidence” in reports that DHEA administration results in significant improvement in libido or sexual function, serum lipids, serum glucose, weight, body mass index, or bone mineral density in postmenopausal women with normal adrenal function due to imprecision, risk of bias, and inconsistencies across randomized controlled trials (Elraiyah et al., 2014).

4.2 The PAQUID Research Program

The PAQUID Research Program was a prospective cohort study of mental and physical aging in a representative sample of elderly subjects residing in south-west France (the Gironde “Département”) (Berr, Lafont, Debuire, Dartigues, & Baulieu, 1996; Mazat et al., 2001). The subjects were followed for 4 and 10 years after their baseline-circulating DHEA levels were measured, looking at a variety of functional, psychological, and mental status measures. Men displayed more rapid declines in circulating DHEA after age 65 than women, confirming the notion of age-related declines in circulating DHEA levels in both sexes. A number of measures of normal activities of daily living, such as drug medication utilization, confinement, dyspnea, depression, poor subjective perception of health, and life satisfaction were assessed over a 4-year period. Women who had lower levels of DHEA/DHEA-S demonstrated on average lower levels of these functional markers, while there was less correlation in men. For men, lower DHEA-S levels were significantly associated with increased short-term mortality at 2 and 4 years after baseline measurement. At 10 years, there were reliable associations of lower circulating DHEA-S levels with increased death in male smokers; death was associated with various types of cardiovascular disease endpoints (Mazat et al., 2001).

4.3 DHEA and Pulmonary Hypertension

Another area of interest to Baulieu and coworkers (Debonneuil et al., 2006; Dumas de La Roque et al., 2012) was the impact of DHEA supplementation on pulmonary hypertension in patients with chronic obstructive pulmonary disease (PH-COPD). In a murine survival study in which mice were made hypoxic with 50% oxygen for prolonged periods, DHEA supplementation protected against pulmonary hypertension (Debonneuil et al., 2006). This was followed by a human subjects pilot experiment where eight subjects with PH-COPD received 200mg DHEA daily for 3 months

(Dumas de La Roque et al., 2012), displayed improved performance on a 6-min walk test, increased lung carbon monoxide diffusing capacity (DLCO % predicted), and improved pulmonary hemodynamics, thereby, reversing chronic hypoxia-induced pulmonary hypertension. This group also studied the effects of DHEA on human pulmonary arterial smooth muscle cells to identify its mechanism of action under hypoxia in vitro. Interestingly, DHEA, nonmetabolizable 3β -methyl- Δ^5 -androst-17-one, T, and E2 were all active in stimulating the increase in HIF-1 α (Dessouroux et al., 2008). These sterols appear to increase accumulation of HIF-1 α protein through a posttranslational process, as HIF-1 α mRNA levels were unchanged in the presence of DHEA and the other compounds. Surprisingly, there are, to our knowledge, no reports, other than ours (Teng et al., 2014), of DHEA regulation of miRNA expression in any tissue. This is a clear gap in knowledge, and future studies will need to assess direct DHEA effects vs effects of DHEA metabolites.

4.4 DHEA and Female Fertility

The number and quality of oocytes retrieved during in vitro fertilization (IVF) is an important parameter for successful fertilization. There have been many studies over the past decade on DHEA supplementation for IVF procedures to improve oocyte retrieval in women who do not respond well to gonadotropin-induced oocyte maturation. The results appear promising yet are not consistent across trials. Two separate trials support DHEA supplementation can improve oocyte retrieval (Kara, Aydin, Aran, Turktekin, & Ozdemir, 2014; Tsui et al., 2015), yet improved pregnancy rates were reported for only one trial (Tsui et al., 2015). A meta-analysis of eight trials reported between 2006 and 2014 concluded that DHEA supplementation improves pregnancy rates without significant improvement in oocyte retrieval or quality (Li et al., 2015). A newly reported prospective study showed that DHEA supplementation at 25 mg three times per day for 8 weeks resulted in increased serum T levels, and AR and FSHR mRNA levels in granulosa cells, that were correlated with an increase in the number and quality of oocytes compared to the control group without DHEA supplementation; however, there was no improvement for the in vitro fertility outcomes (Hu et al., 2017).

4.5 DHEA and Cardiovascular Function and Well-Being

Yen and Coworkers (Yen, 2001) have performed several human studies evaluating the role of DHEA supplementation on overall well-being and

cardiovascular benefits in human subjects. The strongest set of data deal with the correlation in men over age 50 of circulating DHEA-S levels being an independent and inversely related to death from any cause and death from cardiovascular disease (Barrett-Connor et al., 1986), a result similar to that of Baulieu and coworkers (Mazat et al., 2001). The studies from Yen's group also identified changes in serum insulin-like growth factor 1 (IGF-1) and IGF-binding protein-1 (IGF1-BP) caused by DHEA supplementation in aged humans (Morales, Nolan, Nelson, & Yen, 1994). Increased bioavailability of IGF-1 was proposed to enhance the function of the immune system accounting for the benefits of DHEA in HIV and other immune therapies (Khorram, Vu, & Yen, 1997). However, Baulieu and coworkers (Raynaud-Simon et al., 2001) performed several other clinical trials that showed a lack of correlation between plasma DHEA/DHEA-S and IGF-1 levels. Similarly, only modest effects on body weight maintenance were observed in aging males, but little effect for aging females (Morales et al., 1998). In addition, the link between these biomarkers and the mechanism of DHEA action was not conclusively demonstrated and the results were modest in magnitude.

Most critics decry the lack of large numbers of subjects in the clinical trials cited, the modest changes seen, and express concern about hormone-sensitive cancers in men and women (Labrie, 2010a). However, the studies by Yen (Yen, 2001) and by Baulieu and coworkers (Baulieu et al., 2000; Mazat et al., 2001) showed no adverse effects from taking DHEA-S at a dosage of 50 mg daily. If DHEA were to have medical utility, much more sophisticated randomized, placebo-controlled trials in large cohorts of aging humans would be required to prove efficacy and safety. This approach will be weighed against the expense to continue such studies, unless it were supported by a pharmaceutical company documenting efficacy for a regulatory agency.



5. THE FUTURE

From a casual evaluation of the human studies on DHEA, there are a few areas where one might suggest the appropriate application of DHEA and DHEA-S as a therapeutic regimen. Clearly, the declines in endocrine function seen during menopause in women (Labrie, 2010b), such as vaginal atrophy, are an area where DHEA-S therapy may have significant impact. Considerable clinical application has been provided in gynecological medicine since the 1940s due to the direct clinical application of these steroids to

ameliorating symptoms of menopause (Labrie, 2010a). Indeed, Vagifem (E2) is routinely prescribed to alleviate symptoms of vaginal epithelial atrophy in postmenopausal women (Chollet, 2011). Several other areas, such as pulmonary hypertension, SLE, Crohn's disease and ulcerative colitis, IVF, and immune modulation may be worthy of consideration of further research (see Table 2), but many more clinical trials in aged individuals will be required and compared to other therapies before the full utility of DHEA/DHEA-S treatment will be proven. For many of the other conditions, other therapeutic or practice applications will need to come forward instead of DHEA therapy. In addition, there are known adverse effects of DHEA supplementation, including acne, embryo virilization in pregnancy, and endocrine-sensitive cancers. This does not mean that understanding the biology and normal biochemistry and physiology of DHEA and DHEA-S is not important. Understanding the various receptors and binding proteins that DHEA interacts with is important for understanding how it functions and possibly can be a tool in understanding new "receptors" for DHEA as described in a chapter of this volume (Clark et al., 2017). However, in the face of the changing health care system in the United States, it does not seem likely that this steroid as an "orphan drug" will ever be used extensively in human medicine except for those applications where efficacy has strong promise as reviewed earlier. World War II and the effect it had on Schering AG prevented it from being tested rigorously in the clinic like other pharmaceutical agents.

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