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REVIEW

The Origin of 7α-Hydroxy-Dehydroepiandrosterone and Its Physiological Role: a History of Discoveries

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Summary

Nearly 60 years has elapsed since the first isolation and identification of 7α-hydroxy-dehydroepiandrosterone, and in that time much information has been gained on its occurrence, metabolism, ontogeny, immunomodulatory activity, cell proliferation, cortisol control in local tissues and neuroactivity. Additional knowledge about this steroid may elucidate its role in obesity, neurodegenerative disturbances such as Alzheimer's disease, or psychiatric disorders such as schizophrenia or depression. This review aims to provide a comprehensive summary of the available literature on 7α-hydroxy-dehydroepiandrosterone.

Key words

Dehydroepiandrosterone • 7α-hydroxy-dehydroepiandrosterone • Neurosteroid • Occurrence • Immunomodulatory effects • CYP7B • 11β-hydroxysteroid dehydrogenase

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Early studies

7α-hydroxy-dehydroepiandrosterone (3β,7α-di-hydroxy-androst-5-en-17-one; 7-OH-DHEA), known initially from the microbial transformation of dehydroepiandrosterone (DHEA), was first isolated from human material by Okada *et al.* (1959) in the urine of a patient with adrenal carcinoma. In 1961 we published a simple method of 7-hydrox-DHEA synthesis that yielded both α and β isomers with a prevalence of the α-epimer (Stárka and Syhora 1960, Stárka 1961). The crystalline compound obtained enabled us to perform the chromatographic isolation and identification of 7α-OH-DHEA, and in minor concentrations also of the 7β-isomer, in the urine (Stárka *et al.* 1962) and plasma (Stárka and Hampl 1964) of healthy men and women, as well as to study the hepatic (Stárka and Kůtová 1962) and extrahepatic (Šulcová and Stárka 1963, Stárka 1965) 7-hydroxylation of DHEA. 7-hydroxylation was found to be common in various organs of experimental animals (rats, frogs, horses), increasing in the order adrenals – muscle – heart – liver – lung – spleen (Šulcová and Stárka 1963). The ontogeny of 7-OH-DHEA was studied in the human embryo, chorion, amniotic epithelium and amnion (Šulcová *et al.* 1967, Šulcová *et al.* 1968, Šulcová *et al.* 1976, Šulcová *et al.* 1982), with 7-hydroxylation of DHEA found to be starting at the 7th week of gestation and a maximum occurring at the 22-23rd week. 7-hydroxylation in a rat liver homogenate (Stárka and Kutová 1962) and by hepatic microsomal fraction was described and characterized nearly simultaneously by several authors (Šulcová and Stárka 1968, Heinrichs and Colás 1968, Heinrichs *et al.* 1967).

The further metabolic transformation of 7-OH-DHEA was mainly studied in the liver, where depending on conditions the oxidation yielded 7-oxo-DHEA, 7α-hydroxy-androst-4-ene-3,17-dione and 7α-hydroxy-testosterone, whereas incubation of 7-oxo-DHEA with rat liver slices led to the reduction of the 7-oxo-group under the formation of 7α- and 7β-hydroxy-derivatives at an approximate ratio of 1:1 (Hampl and Stárka 1967). We also studied the epimerization of 7α/β-hydroxy-DHEAs and of steroid allyl-alcohols in general (Hampl and Stárka

1969). Hepatic 7-hydroxylation and formation of the 7-oxo-derivative was also found in human embryos in the 7th week of gestation and later (Šulcová *et al.* 1967). The formation of sulphate, either by sulphatation of the 3β-hydroxy-group of 7-OH-DHEA or direct 7-hydroxylation of DHEA-sulphate, was then described in detail (Stárka *et al.* 1967). Aromatization of 7-OH-DHEA occurs in the ovary and placenta (Cedard *et al.* 1964, Janata *et al.* 1965, Stárka *et al.* 1966). Human skin was found to be an important organ for 7-hydroxylation (Faredin *et al.* 1969), and intensive 7-hydroxylation of DHEA was found in a mammary carcinoma (Couch *et al.* 1975). Later, the relationship of 7-OH-DHEA in plasma to the stage of mammary carcinoma was demonstrated (Skinner *et al.* 1980).

After the pioneering research on 7-OH-DHEA in the sixties, nearly one generation passed before major further discoveries were made showing the importance of this steroid. Research was accelerated by the hypothesis that DHEA is a „hormone of youth“ and that its metabolites could participate in this role (Baulieu 1996).

Enzyme system responsible for 7-hydroxylation of DHEA

The 7-hydroxylation of dehydroepiandrosterone was later confirmed in various tissues (adrenals, testis, liver), including the brain (Akwa *et al.* 1992, Akwa *et al.* 1993, Doostzadeh and Morfin 1996, Doostzadeh *et al.* 1997, Rose *et al.* 1997, Morfin and Stárka 2001, Chalbot and Morfin 2005a, Chalbot and Morfin 2012) and adipose tissue (Khalil *et al.* 1993, Khalil *et al.* 1995). The metabolism of DHEA and related 7-hydroxylated derivatives in human liver S9 fractions (Chalbot and Morfin 2005b) and in specific regions of the brain was also described (Weil-Engerer *et al.* 2003, Li and Bigelow 2010).

The enzyme system responsible for the 7-hydroxylation of DHEA was characterized in more detail in the liver, brain and prostate (Tabei *et al.* 1975, Doostzadeh and Morfin 1966, Doostzadeh *et al.* 1997, Doostzadeh *et al.* 1998, Attal-Khémis *et al.* 1998b, Robinzon *et al.* 2004, Chalbot and Morfin 2005a,b, Chalbot and Morfin 2006, Kim *et al.* 2004, Trap *et al.* 2005, Martin *et al.* 2001). Different P450s were found to be involved in the 7α- and 7β-hydroxylation of DHEA, and that in addition to CYP7B1 7-hydroxylase (identical to cholesterol 7-hydroxylase), CYP7B2 also takes part in the 7-hydroxylation of DHEA. A comparison of these findings with those obtained with brain microsomes suggested that tissue-specific P450 species are responsible for the 7α- and 7β-hydroxylation of DHEA (Doostzadeh *et al.* 1998). Microsomes contained most of the activity, except for in the brain where mitochondrial activity was primary (Doostzadeh and Morfin 1996). The system responsible for the 7-hydroxylation of 5-ene-steroids was fully characterized (Stapleton *et al.* 1995, Rose *et al.* 1997, Rose *et al.* 2001). It was concluded that Cyp7b is a 7α-hydroxylase participating in the synthesis of the neurosteroids 7α-hydroxy-DHEA, and 7α-hydroxy-pregnenolone in brain. This system differs from cholesterol 7-hydroxylase, and genomic Southern analysis has suggested that a single gene corresponding to CYP7B1 (also known as hct-1) is present in the mouse, rat, and human. CYP7B1 is unusual in that, unlike all other CYPs described until now, the primary site of expression is in the brain. Findings suggest that nuclear factor-κB (NF-κB) and activator protein AP-1 are involved in the tumor necrosis factor-α (TNF-α) - enhanced formation of the dehydroepiandrosterone metabolite 7α-OH-DHEA (Dulos *et al.* 2005). The ontogeny of the 7-hydroxylation system was also mapped in the mouse embryo (Bean *et al.* 2001).

For the preparation of pure 7-OH-DHEA, the 7-hydroxylation of DHEA in *Saccharomyces cerevisiae* (Vico *et al.* 2002) and *Mucor racemous* (Li *et al.* 2005) were used, and it was proposed that this system may reflect the conservation of an early signaling pathway of non-enzymatic reactions (Lathé 2002).

The effects of 7-OH-DHEA

As could be expected from the fact that molecular oxygen is essential for enzymatic 7-hydroxylation, antioxidant activity was found for DHEA and 7-OH-DHEA (Pelissier *et al.* 2004). The latter steroid exerted its anti-oxidant effect earlier than DHEA and mainly in the liver. As DHEA was found to possess an anti-glucocorticoid activity, it was crucial to determine whether its 7-oxygenated metabolites also exert such an effect. The anti-glucocorticoid activity of 7-OH-DHEA was demonstrated e.g. on the viability of plaque forming cells of cultured murine spleen lymphocytes incubated with dexamethasone (Hampl *et al.* 2000b). As for DHEA, no specific receptors were found for 7-OH-DHEA and no binding to the glucocorticoid receptors could be demonstrated (Stárka *et al.* 1998, Muller *et al.* 2004, Muller *et al.* 2006).

An important contribution to the question of the role of 7-OH-DHEA was made by Chalbot and Morfin (2006). First, they demonstrated that 7-hydroxylated steroids produced in human tonsils enhance the immune response to tetanus toxoid and *Bordetella pertussis* antigens (Lafaye *et al.* 1999), and that second, the dexamethasone-induced apoptosis of mouse thymocytes is prevented by native 7α-hydroxysteroids (Chmielewski *et al.* 2000). A similar effect was observed in murine spleenocytes (Šterzl *et al.* 1999). Several authors (Morfin and Courchay 1994, Morfin *et al.* 2000, Hampl *et al.* 1997, Hampl *et al.* 2001) published further proof that 7-hydroxylated steroids are involved in a process that may participate in the physiological regulation of the body's immune response. Immunomodulatory cytokines in seminal plasma correlated with the content of 7-OH-DHEA (Hampl *et al.* 2000a,b, Pohanka *et al.* 2002, Šterzl *et al.* 2003). In rats with colitis, anti-inflammatory effects and changes in prostaglandin patterns were produced even more intensively by 7-hydroxy-epiandrosteron, a metabolite of 7-OH-DHEA (Hennebert *et al.* 2007c). An anti-proliferative activity of 7-oxygenated-DHEA metabolites that is not induced by inhibiting G6PD (glucose-6-phosphate dehydrogenase) or HMGR (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) activity alone was also observed (Yoshida *et al.* 2003).

7-OH-DHEA in the brain

Numerous authors have paid attention to the presence and role of 7-oxygeneted dehydroepiandrosterone derivatives in the brain (for review see Morfin and Starka 2001).

7-hydroxylated derivatives of dehydroepiandrosterone were found in the human ventricular cerebrospinal fluid (Stárka *et al.* 2009, Kancheva *et al.* 2011) and were compared with serum levels (Kancheva *et al.* 2010) in women with hydrocephalus. In shunt cerebrospinal fluid, 7-OH-DHEA could be even used as a prognostic factor for the success of surgical therapy (Sosvorová *et al.* 2012, Sosvorová *et al.* 2015a,b).

Particular attention has been paid to the role of 7-OH-DHEA in the brain as a neuroactive steroid. The pioneer works in this field were reviewed by Morfin and Stárka (2001). DHEA enhances memory and immune function but has no known dedicated receptor; local metabolism may govern its activity (Rose *et al.* 2001, Stárka *et al.* 2015). There were several contributions to knowledge on the localization, production in various areas of the brain, the conditions for 7-hydroxylation and further metabolism and the effects as a neurosteroid of 7-OH-DHEA (Jellinck *et al.* 2001, Jellinck *et al.* 2005, Li and Bigelow 2010, Rose *et al.* 2001, Kazihnitková *et al.* 2004). In contrast to DHEA, 7-hydroxylated derivatives were shown to mediate neuroprotection (Jellinck *et al.* 2005, Chalbot and Morfin 2005a,b, Pringle *et al.* 2003, Yau *et al.* 2003, Yau *et al.* 2006).

Several very important findings were that the interconvertible 7-oxygenated Δ^5-steroids, namely 7α-, 7β-hydroxy-DHEA and 7-oxo-DHEA, can be substrates for 11β-hydroxysteroid dehydrogenase type I (11β-HSD), and so 7-OH-DHEA and other 7-hydroxylated C_{19}-steroids function as factors maintaining the balance of local cortisol and cortisone concentrations (Hennebert *et al.* 2007a,b,c, Hennebert *et al.* 2009, Muller *et al.* 2006). These important interconversions locally controlling glucocorticoid levels in various tissues were also confirmed by other authors (Robinzon *et al.* 2003). The balance between 7β-hydroxy- Δ^5-C_{19} steroids and their 7α-hydroxy- counterparts is regulated by type 1 11β-hydroxysteroid dehydrogenase (HSD11B1), which is capable (in addition to catalyzing the conversion of inactive cortisone to bioactive cortisol) of converting the 7α-hydroxy- Δ^5-C_{19} steroids *via* 7-oxo-steroid to their 7β-hydroxy- counterparts. This view was supported by the findings (Steckelbroeck *et al.* 2002) of high levels of CYP7B1 mRNA in brain tissue as well in combination with the ubiquitous presence of 7α-hydroxylase activity in the human temporal lobe, which led to the assumption of a neuroprotective function of the enzyme such as regulation of the immune response or counteracting the deleterious effects of neurotoxic glucocorticoids, rather than a distinct brain specific function such as neurostimulation or neuromodulation. However, the role of these steroid transformations has been questioned, and it has been suggested that other as-yet unknown mechanisms responsible for the anti-glucocorticoid activity of DHEA and its metabolites may be found (Jellinck *et al.* 2001, Gottfried-Blackmore *et al.* 2013). Investigations of the metabolism of DHEA in E(t)C neuronal cells suggest that other alternate mechanisms than 11β-HSD must also be at play to explain the *in vivo* anti-glucocorticoid properties of DHEA and its 7-hydroxy-metabolites (Gottfried-Blackmore *et al.* 2013). 7-hydroxygenated metabolites of DHEA might be responsible for some of the functions previously ascribed to estrogens in the brain (Jellinck *et al.* 2001).

Local control of the cortisol/cortisone ratio by 7-oxygenated DHEA metabolites was suggested as a possible factor in some neurodegenerative diseases such as Alzheimer´s dementia (Kim *et al.* 2003, Bičíková *et al.* 2004, Vaňková *et al.* 2016) and psychiatric disorders such as depression and anxiety (Dušková *et al.* 2015, Hill *et al.* 2016), schizophrenia (Bičíková *et al.* 2011) and premenstrual syndrome (Dušková *et al.* 2011). 7α-hydroxy-dehydroepiandrosterone is especially abundant in the brain, and in agreement with recent opinion plays a neuroprotective and immunoprotective role. 7-OH-DHEA has also been found in cerebrospinal fluid (Kancheva *et al.* 2010, Kancheva *et al.* 2011, Sosvorová *et al.* 2015a,b). Decreased levels of DHEA were found in the cerebrospinal fluid of patients with Alzheimer´s disease (AD), whereas its 7-oxygenated metabolites were not significantly changed (Kim *et al.* 2003). Increased 7-OH-DHEA was found in the plasma of AD patients (Kim *et al.* 2003, Attal-Khémis *et al.* 1998a), whereas others found lower levels in serum (Bičíková *et al.* 2004, Vaňková *et al.* 2016). Changes in the ratio of 7α/7β-hydroxy-DHEA were seen in patients with dementia, and this ratio was sufficient for the differentiation between vascular and Alzheimer´s dementia (Kim *et al.* 2003). Levels of 7-OH-DHEA were found to be lower in the plasma of patients with Alzheimer's dementia (AD) than in controls, and even lower than in the plasma of patients with vascular dementia (Bičíková *et al.* 2004, Hampl and Bičíková 2010).

7-OH-DHEA has been measured in the individual brain regions of AD patients and aged non-demented controls. A significantly higher synthesis of 7α-hydroxy-DHEA in the frontal cortex was observed compared with that in other brain regions. In addition, a trend toward a significant negative correlation was found between the density of cortical amyloid deposits and the amount of 7α-hydroxy-DHEA formed in the frontal cortex (Weill-Engerer *et al.* 2003). Additionally, a reduced (50 %) activity of 7-hydroxylating CYP7B system was found in the hippocampus of primates with AD (Yau *et al.* 2003).

Other effects of 7-OH-DHEA

Since one close metabolite of 7-OH-DHA is 7-oxo-DHEA (Marwah *et al.* 2002), which is claimed to possess some thermogenic activity as an ergosteroid (Lardy *et al.* 1995), it is possible that at least some of the effects of 7-OH-DHEA are actually exerted by its metabolites.

Another related steroid, 5-androstene-3β,7β,17β-triol, exhibits glucocorticoid-opposing and immune-modulating activity (Ahlem *et al.* 2011), and because its plasma levels positively correlate with BMI in healthy men and women, the authors suggested its compensatory role in preventing the development of metabolic syndrome (Auci *et al.* 2011). 5-androstene-3β,7β,17β-triol (β-AET), an active metabolite of dehydro-epiandrosterone (DHEA), reversed the glucocorticoid induced suppression of IL-6, IL-8 and osteoprotegerin production (Malik *et al.* 2010). This steroid also influences estrogen receptor beta signaling (Pettersson *et al.* 2010).

Recently, attention has been given to various situations in which the levels of 7-OH-DHEA are different from control samples, as e.g. in the course of gravidity and following childbirth (Hill *et al.* 2010), during the female menstrual cycle in connection with changes of mood (Dušková *et al.* 2011), obesity (Sedláčková *et al.* 2012, Máčová *et al.* 2014), and during adrenal function testing by the ACTH or hypoglycemic tests (Dušková *et al.* 2016).

Methods for the analysis and production of 7-OH-DHEA

The first RIA of 7-OH-DHEA was described by Skinner *et al.* (1977). Lapčík later used this method to describe the course of plasma levels of men and women during their life spans, finding a remarkable decrease with age after 40 (Lapčík *et al.* 1998, Lapčík *et al.* 1999, Hampl *et al.* 2001). Presently, LC/MS or GC/MS methods are preferred (Hampl *et al.* 2002, Hill *et al.* 2001, Li *et al.* 2010, Sosvorová *et al.* 2015a, Matsuzaki *et al.* 2004).

Simplified chemical approaches leading to the production of 7α-/7β-hydroxy-DHEA in quantities that made them readily available to researchers, and the production of isotope-labeled compounds, ^{2}H-, ^{3}H-, and ^{14}C-labeled 7α-/7β-hydroxy-DHEA, were summarized by Feroud *et al.* (2012).

Conflict of Interest

There is no conflict of interest.

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