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Review

Dehydroepiandrosterone, its metabolites and ion channels

M. Hill*, M. Dušková, L. Stárka

Steroid Hormone Unit, Institute of Endocrinology, Národní třída 8, Prague 116 94, Praha 1, CZ 116 94, Czech Republic

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ABSTRACT

This review is focused on the physiological and pathophysiological relevance of steroids influencing the activities of the central and peripheral nervous systems with regard to their concentrations in body fluids and tissues in various stages of human life like the fetal development or pregnancy. The data summarized in this review shows that DHEA and its unconjugated and sulfated metabolites are physiologically and pathophysiologically relevant in modulating numerous ion channels and participate in vital functions of the human organism. DHEA and its unconjugated and sulfated metabolites including 5α/β-reduced androstane steroids participate in various physiological and pathophysiological processes like the management of GnRH cyclic release, regulation of glandular and neurotransmitter secretions, maintenance of glucose homeostasis on one hand and insulin insensitivity on the other hand, control of skeletal muscle and smooth muscle activities including vasoregulation, promotion of tolerance to ischemia and other neuroprotective effects. In respect of prevalence of steroid sulfates over unconjugated steroids in the periphery and the opposite situation in the CNS, the sulfated androgens and androgen metabolites reach relevance in peripheral organs. The unconjugated androgens and estrogens are relevant in periphery and so much the more in the CNS due to higher concentrations of most unconjugated steroids in the CNS tissues than in circulation and peripheral organs.

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Contents

* Corresponding author. Tel.: +420 224 905 267; fax: +420 224 905 325.
E-mail addresses: mhill@endo.cz (M. Hill), mduskova@endo.cz (M. Dušková), lstarka@endo.cz (L. Stárka).

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1. Introduction

Dehydroepiandrosterone and a variety of its free and sulfated derivatives are efficient neuromodulators not only in the central nervous system but also in peripheral tissues. This review focuses on the effects of these steroids at ion channels and attempts to estimate the actual physiological relevance of steroid neuromodulators taking into account their concentrations in body fluids and tissues and their pharmacological characteristics. As will be documented further in the text, the androgen and estrogen neuromodulation is essential for important physiological and pathophysiological processes like the functioning of kisspeptin-hypothalamic-pituitary gonadal axis, regulation of glucose homeostasis, vasomodulation, hormonal secretion, regulation of gastrointestinal tract or urogenital functioning.

2. Nicotinic acetylcholine receptors (nAChR)

Nicotinic acetylcholine receptors (nAChR) create ligand-gated ion channels in neuronal membranes on both pre- and postsynaptic sites [1,2] functioning in both central- (CNS) and peripheral (PNS) nervous systems. Although the key ligand of nAChR is the neurotransmitter acetylcholine (ACh), these receptors may be also opened by nicotine [3]. Nicotine and choline are subtype-specific, and function as both agonist and antagonist depending of the nAChR subtype (see review [4]). All nAChR are permeable to Na^+ (influx) and K^+ (efflux) and some subunit combinations also allow the Ca^{2+} influx (the α7 subtype) [5,6]. Besides the cholinergic neurotransmission, the nAChR participate in the regulation of synaptic release of further neurotransmitters like dopamine, glutamate, GABA, and norepinephrine (see reviews [7]).

The nAChR subunits are encoded by CHRNA1–CHRNA10 (α1–α7, α9, α10 subunits), CHRNB1–CHRNB1 (β1–β4 subunits), CHRNG (γ subunit), CHRND (δ subunit), and CHRNE (ε subunit) genes [8] [9]. The nAChR subunits form pentameric receptor subtypes. The α7 and α9 subunits form the class of homomeric subtypes containing only the α subunits, while the α2–α6, and β2 form the class of heteromeric subtypes containing both α and β subunits (α2–α6 and β2–β4). The most common subtypes of nAChR are low-affinity homomeric α7 subtype and high affinity (for nicotine and acetylcholine) α4β2* (α4β2-containing) subtypes (about 90%), and particularly the α4β2 subtype formed in the 2α:3β stoichiometry. Generally, in heteromeric subtypes, the sensitivity to agonist depends not only on the presence of individual subunits but also on the subunit stoichiometry (see reviews [7,10,11]).

CHRNA1, CHRNA6, CHRNA7, CHRNA9, CHRNA10, CHRNB2–CHRNB4, CHRND, and CHRNE are nearly ubiquitously expressed. Alternatively, when compared with other tissues, the expression of CHRNA2 is about three and two times higher in heart and thyroid, respectively, CHRNA3 expression is by more than two orders of magnitude higher in pineal gland, retina, and thymus, CHRNA4 is about thrice more expressed in the skeletal muscle and twice in the heart and liver, the uterine expression of CHRNA5 is about three times higher, CHRNB1 expression is about twice higher in the heart and skeletal muscle, and CHRNG exhibit more than twice higher expression in cardiac myocytes [8].

The α7 nAChR are significantly higher in fetal CNS than in the adult one and show a pronouncedly increasing expression in various regions during the first trimester of human pregnancy [12]. These findings together with markedly elevated levels of fetal nAChR-inhibitory estrogens (as compared to the situation in adult non-pregnant subjects) point to the importance of α7 nAChR in the fetal neurodevelopment.

In rat superior cervical ganglionic neurons, some endogenous steroids like cortisol, estradiol ($IC_{50} \approx 28$ μM, at 10 μM of acetylcholine), androsterone ($IC_{50} \approx 28$ μM at 10 μM of acetylcholine and 10 μM of bicuculine) as well as aldosterone metabolites inhibit the nAChR-mediated responses. The inhibition potency is highest for the DHEA metabolite androsterone but its levels in the human circulation are relatively low (~1 nM) [13]. Nevertheless, the relatively low polarity of this saturated steroid facilitating its transport across the blood brain barrier may indicate its higher concentrations and therefore higher relevance in the CNS.

Liu et al. [14] reported a significant dose-dependent inhibition of norepinephrine secretion in bovine adrenal chromaffin cells by DHEAS at concentrations common in human circulation (10 μM). DHEAS inhibits the norepinephrine release induced by activators of $[Ca^{2+}]_i$ and Na^+. DHEA also suppresses K^+-induced norepinephrine secretion but without influencing the $[Ca^{2+}]_i$ rise [15].

DHEAS and estradiol inhibit the α4β2 nAChR with a slow kinetics as was demonstrated on the rat neuronal α4β2 nAChR expressed in human embryonic kidney 293 cells. While estradiol (IC_{50} = 12 μM) is effective at supraphysiological concentrations, the DHEAS inhibition is effective at concentrations common in the human circulation (IC_{50} = 7.0 μM) [16]. In contrast to the previous