STEROIDS 72 (2007) 792–801

available at www.sciencedirect.com

ScienceDirect

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

The identification and simultaneous quantification of neuroactive androstane steroids and their polar conjugates in the serum of adult men, using gas chromatography–mass spectrometry

L. Kancheva[a], *M. Hill*[a,*], *H. Včeláková*[a], *J. Vrbíková*[a], *T. Pelikánová*[b], *L. Stárka*[a]

[a] *Institute of Endocrinology, Národní třída 8, Prague CZ 116 94, Czech Republic*
[b] *Diabetes Center, Institute of Clinical and Experimental Medicine, Vídeňská 1958/9, Prague 140 21, Czech Republic*

ARTICLE INFO

Article history:
Received 2 October 2006
Received in revised form
28 June 2007
Accepted 29 June 2007
Published on line 10 July 2007

Keywords:
Neuroactive steroids
Human
Serum
Androgens
GC–MS

ABSTRACT

Certain androstane steroids (AS) modulate ionotropic receptors, as do the pregnane steroids. Whereas women produce significant amounts of neuroactive progesterone metabolites, the steroid neuromodulators in men originate mainly from the 3-oxo-4-ene C_{19}-steroids, which are converted to their 3α- and 3β-hydroxy-5α/5β-reduced metabolites. The neuromodulating effects of AS prompted us to monitor circulating levels of the steroids to estimate metabolic pathways in the periphery that may influence brain concentrations of AS. Hence, the serum levels of 20 steroids and 16 steroid polar conjugates including 17-oxo- and 17β-hydroxy-derivatives of 5α/β-androstane-3α/β-hydroxy-androstane steroids were quantified in 15 men (16–62 years of age) using GC–MS. The conjugated AS for the most part reached micromolar concentrations, these being two or three orders of magnitude higher than those of the free steroids. The ratios of conjugates to free steroids were one to two orders of magnitude higher than the values for the corresponding pregnane steroids. This data suggested that conjugation may considerably restrain the transport of free AS from the periphery into the central nervous system.

© 2007 Elsevier Inc. All rights reserved.

1. Introduction

Like the pregnane steroids (PS), androstane steroids (AS) are known as modulators of ionotropic receptors [1–4]. The most recognized membrane receptors modulated by AS are the receptors of type A γ-aminobutyric acid ($GABA_A$-r), responsible for the chloride influx into the neuron [3–6]. The receptors are positively modulated by PS and AS that have a hydroxy group in the 3α-position [4,6]. Additionally, the 3β-PS compete with 3α-PS for the binding sites on the $GABA_A$-r [7–9], and a similar effect could be expected in the 3-AS. Among the PS, the 3α-isomers shorten the period of paradoxical sleep, attenuate the release of acetylcholine in the neocortex and hippocampus, suppress neurogenesis and cause the deterioration of the spatial memory. These effects occur due to modulation of $GABA_A$-r [10]; similar effects are likely in the case of 3α-AS [3]. The 3α-androstane steroids, such as androsterone (3α-hydroxy-5α-androstan-17-one, A3α5α) and 5α-androstane-3α,17β-diol (A3α5α17β) stimulate $GABA_A$-r, while the 3β-isomers are inoperative, as are the isomers with a hydroxy-group in the 17α-position [6]. The polar conjugates of PS and AS exert the opposite effect via the negative

* *Corresponding author*. Tel.: +420 2 24905 267; fax: +420 2 24905 325.
E-mail addresses: lkancheva@endo.cz (L. Kancheva), mhill@endo.cz (M. Hill), hhavlikova@endo.cz (H. Včeláková), jvrbikova@endo.cz (J. Vrbíková), tepe@medicon.cz (T. Pelikánová), lstarka@endo.cz (L. Stárka).
0039-128X/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2007.06.006

modulation of $GABA_A$-r on specific sites that are different from those binding unconjugated 3α-PS and 3α-AS [4].

The experimental data indicates that the nervous system is influenced by two different pools of steroids, the first depending on peripheral glands and the second originating directly in the nervous system [11]. In women, the formation of the most abundant GABA-ergic steroid, allopregnanolone (3α-hydroxy-5α-pregnan-20-one, P3α5α), primarily reflects ovarian activity, particularly in pregnancy and in the luteal phase of the menstrual cycle. Women in the follicular phase, postmenopausal women, men and children produce most of the P3α5α precursors in the adrenal cortex [12].

In neuroactive androstane metabolites, a direct adrenal cortical secretion accounts for a minor proportion of the serum level of A3α5α, A3α5α17β, and 5α-dihydrotestosterone (DHT5α) but serum A3α5α is derived mainly from precursors from the adrenal cortex in both sexes (Fig. 1). As reported in the study of Labrie et al. [13], percutaneously applied DHEA is converted in specific intracrine tissues to 3α/β5α17-oxo/β androstane metabolites that are locally metabolized to polar conjugates, which can be measured in relatively high concentrations in the peripheral blood. After DHEA administration, testosterone showed a significant change in women only. DHT5α was unchanged in both sexes and A3α5α17β showed only a negligible increase. The unconjugated A3α5α showed a slight increase in both sexes but a pronounced increase was observed in unconjugated 5α-androstane-3β,17β-diol (A3β5α17β) and further conjugated 3(α/β)5α17(-oxo/β) androstane metabolites. Meikle et al. [14] suggested that A3α5α17β, and DHT5α originate largely from testicular steroidal precursors in men and from both adrenal and ovarian precursors in women. These authors also indicated that conjugation of androgens in preparation for their excretion into urine occurs extensively in the liver which has high activity of 5α- and 5β-reductases. Nevertheless, the splanchnic tissues do not secrete DHT5α into peripheral blood. Thus it was suggested that extra-splanchnic tissues form a major quantity of circulating unconjugated 5α-reduced androgens.

It is generally felt that the more lipid-soluble a compound is, the more easily it can gain entry into the cerebrospinal fluid (CSF) space. In spite of this, Marynick et al. [15] reported that the transfer of DHT5α from serum to CSF was minimal but testosterone and estradiol penetrated the blood–brain barrier (BBB) to a significant degree. The serum/CSF ratios of the sex steroids directly correlated with the respective binding affini-

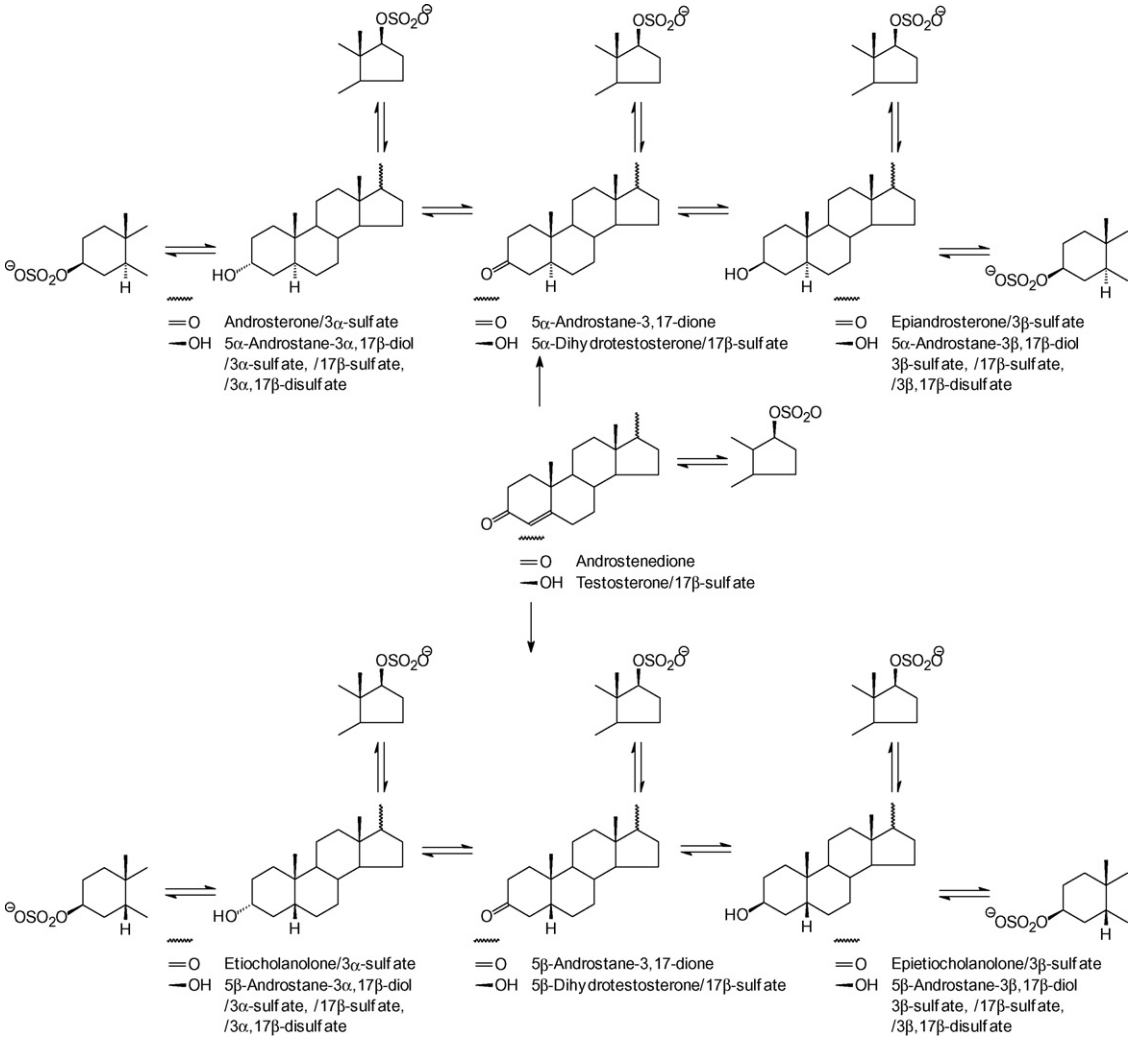

Fig. 1 – The conversion of androstenedione and testosterone to androstane steroids.

Download English Version:

https://daneshyari.com/en/article/2028968

Download Persian Version:

https://daneshyari.com/article/2028968

Daneshyari.com