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Review

Fatty acid esters of steroids: Synthesis and metabolism in lipoproteins and adipose tissue

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Abstract

At the end of the last century ideas concerning the physiological role of the steroid fatty acid ester family were emerging. Estrogens, fatty acylated at C-17 hydroxyl group and incorporated in lipoproteins were proposed to provide antioxidative protection to these particles. A large number of studies involving non-estrogenic adrenal steroids, and their fatty acylated forms, demonstrated their lipoprotein-mediated transport into cells and subsequent intracellular activation, suggesting a novel transport mechanism for lipophilic steroid derivatives. After these important advances the main focus of interest has shifted away from C-19 and C-21 steroids to fatty acylated estrogens. However, interest in their lipoprotein-mediated transport has decreased because only minute amounts of these derivatives were detected in circulating lipoproteins, and their antioxidative activity remained unconfirmed under physiological circumstances. It now appears that the overwhelming majority of estradiol in postmenopausal women resides in adipose tissue, most of it in esterified form. This is poorly reflected in plasma levels which are very low. Recent data suggest that estrogen fatty acid esters probably represent a storage form. The future focus of investigation is likely to be on firstly, the enzymatic mechanisms regulating the esterification and de-esterification of estradiol and other steroids residing in adipose tissue and secondly, on the role of insulin and other hormones in the regulation of these enzymatic mechanisms. Thirdly, as a large proportion of fatty acid esterified C-19 and C-21 non-estrogenic steroids is transported in lipoproteins and as they are important precursors of androgens and estrogens, this field should be investigated further.

Research highlights

► Steroid fatty acid esters are transported in the circulation by lipoproteins. ► A major part of estradiol in the female adipose tissue is in fatty acid esterified form. ► Enzymatic mechanisms regulating the esterification of steroids are of interest.

Introduction

A landmark review was published in 1998 by Richard B. Hochberg [1]. It summarized everything known up to that time of a unique hormone family consisting of lipophilic derivatives of steroids which were transported in the circulation incorporated in lipoprotein particles. These substances were characterized as steroids bound to long-chain fatty acids by an ester bond. They are formed by lecithin:cholesterol acyltransferase (LCAT) in plasma but by different acyltransferases in other tissues. In plasma, cholesterol is the most avidly esterified steroid by LCAT, followed by

adrenal steroids pregnenolone and dehydroepiandrosterone. 17β-Estradiol (estradiol), the principal and most potent estrogen in women, is also esterified with fatty acids in plasma and other tissues. Estradiol fatty acid esters do not bind to estrogen receptors and therefore require to be hydrolyzed to estradiol to exert hormonal effects. As indicated by metabolic studies, this hydrolysis of the ester bond is relatively slow. Accordingly, fatty acid esterified estradiol administered to experimental animals has shown stronger and more sustained estrogenic effects as compared with estradiol.

By 1998 major theories concerning the physiological role of steroid fatty acid esters were emerging [1]. Estrogens containing one or more hydroxyl groups in the aromatic A ring of the molecule exhibited antioxidative activity in lipid–aqueous systems *in vitro* and were proposed to provide antioxidative protection for lipoprotein particles. This was plausible as the estrogens were fatty acylated at C-17 OH group leaving the proposed antioxidative aromatic hydroxyl group at C-3 free (Fig. 1) [1]. In addition, some studies involving non-estrogenic C-19 and C-21 steroids demonstrated that esterified steroids carried in low density lipoprotein (LDL) particles could be internalized into cells *via* lipoprotein receptors, and converted to other biologically active metabolites [1]. The data suggested that esterified steroids had a dual role in lipoproteins. Some of them acted as antioxidants and had therefore antiatherogenic potential. They were also being transported in lipoprotein particles to various tissues in which they could enter the cells and become activated and metabolized further. Also, the first quantitative methods for steroid fatty acid ester determination in blood, ovarian follicular fluid and adipose tissue were developed and initial results raised the possibility that hydrophobic derivatives of steroid hormones might be storage forms.

Section snippets

Human studies: fatty acid esterification of steroids

The enzyme responsible for the esterification of steroid hormones in humans has only been characterized in plasma and ovarian follicular fluid [1]. In these tissues, the esterifying enzyme is LCAT, the same enzyme that esterifies cholesterol. LCAT is known to catalyze the esterification of pregnenolone, dehydroepiandrosterone, 5-androstene-3β,17β-diol (androstenediol) and estradiol [2]. The biosynthesis of fatty acid esters of estriol, a less lipophilic estrogen, was characterized for the first …

Fatty acid esterification of steroids

Early studies carried out in the rats and other experimental animals have shown that a large number of steroids become fatty acylated in various tissues such as the liver, brain and placenta [1]. More recently, Xu et al. studied the esterification of estradiol and other steroids in female rats [18]. In the rat liver, the highest specific estradiol acyltransferase activity was detected in the microsomal fraction, in accordance with previous studies [1], and K_m was 4–6μmol/l for estradiol at the…

Antioxidative effects of fatty acylated estrogens in lipoproteins

All estrogens have a hydroxyl group in the aromatic A-ring, a structural feature which is suggestive of antioxidative activity. Based on that, several laboratories have carried out studies to clarify this issue. Shwaery et al. studied the association of radiolabeled estrogens estradiol, estriol and estrone with LDL in plasma and their effect on the oxidation of LDL *in vitro* [10]. When human plasma was incubated in the presence of 10–100nmol/l of estradiol, corresponding to estrogen…

Metabolism of lipoprotein-associated steroid fatty acid esters

Esterified steroids incorporated in HDL or LDL can be taken up into cells *via* lipoprotein receptors and act as substrates for steroid synthesis. Pioneering studies by Bélanger's group in the 1990s showed that lipoprotein-bound esterified steroids acted as a source of inactive hormones that could be hydrolytically activated following lipoprotein receptor-

mediated intake into cells, as summarized in Hochberg's review [1]: LDL and HDL particles containing ^{3}H-labeled pregnenolone fatty acid ester…

Circulating steroid fatty acid esters

The presence of lipophilic estradiol derivatives in human blood was originally described by Janocko and Hochberg [68], [69]. The same group was the first to quantify hydrolyzed estradiol fatty acid esters in human tissues by a GC–MS method [6]. In this early study, low concentrations of esterified estradiol were detected in blood in four premenopausal women, ranging between 2 and 22% of serum nonesterified estradiol, but higher serum estradiol ester concentrations were reported in three women…

Fatty acid esters of sex steroids in invertebrates

Animals from several invertebrate groups have vertebrate-type sex hormones. However, their biosynthetic pathways have not been fully characterized [95]. When different tissues have been incubated with estradiol, dehydroepiandrosterone or testosterone, the formation of lipophilic steroid conjugates has been reported in several invertebrate groups including molluscs, echinoderms and crustaceans [96], [97], [98], [99]. Some mollusc species appear to synthesize lipophilic steroid conjugates upon…

Conclusions

During the past decade, investigations on the physiological role of steroid fatty acid esters have concentrated on lipophilic estrogen derivatives in man and experimental animals. In contrast, the number of new reports on fatty acid esterified C-19 and C-21 non-estrogenic steroids has become smaller following the successful experimental demonstration in the 1990s of the LDL-mediated transport of these hormones into cells and subsequent intracellular activation. As a large proportion of these…

Disclosure statement

The authors have nothing to disclose.…

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