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Review

Steroid sulfatase inhibitors: A review covering the promising 2000–2010 decade

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ABSTRACT

The steroid sulfatase (STS) plays a major role in the regulation of steroid hormone concentrations in several human tissues and target organs and therefore, represents an interesting target to regulate estrogen and androgen levels implicated in different diseases. In this review article, the emphasis is put on STS inhibitors reported in the fruitful 2000–2010 decade, which consolidated the first ones that were previously developed (1990–1999). The inhibitors reviewed are divided into four categories according to the fact that they are sulfamoylated or not or that they have a steroid nucleus or not. Other topics such as function, localization, structure and mechanism as well as applications of STS inhibitors are also briefly discussed to complement the information on this crucial steroidogenic enzyme and its inhibitors.

Contents

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1. Introduction

Steroidogenesis is a multi-step process that is responsible for the biosynthesis of steroids, which are known to play crucial physiological roles by acting as hormones on a targeted receptor [1–10]. Progestins, glucocorticoids, mineralocorticoids, androgens and estrogens are thus among the most important hormones in humans. From the development of endocrinology, it became clear that efficiently blocking a key enzyme using an inhibitor could modulate the concentration of steroid hormones, thus producing a therapeutic effect. The use of potent 5α-reductase inhibitors [11–15] for treating benign prostatic hyperplasia, and more recently of aromatase inhibitors [16–20] for treating breast cancer are two important realizations that confirmed the interest of targeting one of the enzymes involved in the steroidogenesis pathway [21]. Such success stories are very encouraging for medicinal chemists and stimulated the research and development of potent and selective inhibitors of other key enzymes. Among the enzymes responsible for the biosynthesis of steroidal hormones, 17β-hydroxysteroid dehydrogenases (17β-HSDs), 11β-hydroxysteroid dehydrogenases (11β-HSDs), 17-hydroxylase/17,20-lyase (P450c17) and steroid sulfatase (STS) have been identified for their key physiological functions.

In this review article, we focused on the STS considering its important role in the production of biologically active free hydroxysteroids from abundant sulfated steroids (inactive on steroid receptors and not acting as substrates for other steroidogenic enzymes) (Fig. 1). The manuscript put the emphasis on the STS inhibitors reported in the fruitful 2000–2010 decade. These inhibitors are divided into four categories according to the fact that they are sulfamoylated or not or that they have a steroid nucleus or not. Inside each category, the inhibitors were chronologically reported according to the year of publication (articles and patents) and by research groups. Other topics such as function, localization, structure and mechanism as well as applications of STS inhibitors are also briefly discussed.

1.1. STS (function, localization, structure and mechanism)

Steroid sulfatase (STS) or aryl sulfatase C is a member of the mammalian sulfatase superfamily. The natural substrates of human sulfatases have varying degrees of structural complexity, from simple aromatic molecules to more complex molecules, but the uniqueness of STS (EC 3.1.6.2) is its ability to hydrolyze sulfated steroids to free (unconjugated) hydroxysteroids. Thus, the best known substrates of STS are cholesterol sulfate (CHOLS), pregnenolone sulfate (PREGS), dehydroepiandrosterone sulfate (DHEAS) and estrone sulfate (E1S) (Fig. 2). For these substrates, the K_m values are 2.0, 0.6, 1.7 and 0.8 μM, respectively, and the hydrolysis rates are 1400, 1600, 1000 and 2900 nmol/min/mg of protein, respectively [22]. STS is also able to hydrolyze non-steroidal substrates such as 4-nitrophenol sulfate (NPS) and 4-methylumbelliferone sulfate (MUS), but with lower catalytic potency (K_m = 400 and 800 μM; hydrolysis rate = 4000 and 7000 nmol/min/mg, respectively). This later non-steroidal substrate is sometime used in enzymatic assays for inhibitor screening purposes. STS is not a reversible enzyme and the reverse reaction (hydroxysteroid sulfatation) was done by a different steroidogenic enzyme, the steroid sulfotransferase (EC 2.8.2) [23].

STS is a transmembrane protein, predominantly associated with endoplasmic reticulum, with smaller fractions found in the Golgi and at the cell surface. STS consists of 583 amino acids and the molecular mass of purified STS was found to be approximately 65 kDa depending on the extent of glycosylation [24]. Recent studies have however indicated the existence of a nuclear STS isozyme [25]. The tissue distribution of STS varies considerably between different mammals. In humans, the placenta is the most abundant source of STS, but the enzyme activity was found in numerous other tissues such as adrenal glands, ovary, testis, prostate, skin and brain. STS was also detected in malignant prostate and breast tissues as well as in cancer cell lines (as examples LNCaP, DU-145, PC-3, MCF-7). It was also reported that the expression of STS in some malignant tissues (breast, prostate) is significantly higher than in normal tissues, suggesting a potential role of STS in hormone-dependent cancers. Thus, considering that sulfated steroids are neither ligands of steroid receptors nor active hormones, the inhibition of STS could be a desirable strategy to inactivate the biological functions of steroids, as an example, their mitogenic (proliferative) effect in cancer cells.

From the seventeen human sulfatases identified, the crystal structures of aryl sulfatase A (ARSA), aryl sulfatase B (ARSB) and steroid sulfatase (STS) have been determined [26]. The first two sulfatases are lysosomal and represent soluble forms of the enzyme, whereas the third is a microsomal (membrane) enzyme. The 3D structures of these sulfatases exhibit good homology, and the spatial arrangement of amino acids responsible for the sulfate hydrolysis is virtually identical. Although these three sulfatases have a catalytic polar domain that can be superimposed on each other very well, STS has two trans-membrane domains consisting of two antiparallel hydrophobic alpha helices (~40 Å long). Fig. 3A thus represents the 3D shape of crystallized STS whereas Fig. 3B is a representation of the natural substrate E1S linked in the catalytic site [27]. The hydrophilic (polar) sulfate group is located in the polar area of the catalytic site and the hydrophobic moiety of the steroid (rings B–D) substrate is pointing towards the hydrophobic area of the STS.

The mechanism of the sulfatase ester hydrolysis involves two key elements that are the presence, in all sulfatases, of an α-formylglycine (FGly) and a cation (Ca^{+2}), which are both essential for the catalytic activity [26–28]. The addition-hydrolysis (AH) and transesterification–elimination (TE) mechanisms were proposed based on studies using ARSB and ARSA, respectively. It is however believed that the sulfate hydrolysis proceeds by TE mechanism. Ghosh recently proposed such a TE mechanism for STS involving