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Review Article

Steroid sulfatase inhibitors for the topical treatment of skin disorders

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CONTENTS

Abstract

Inhibition of steroid sulfatase (STS) activity in skin is a potential new treatment strategy for a number of skin disorders, including hirsutism, androgen-dependent alopecia, acne and psoriasis. In skin and its appendages, STS regulates the hydrolysis of dehydroepiandrosterone sulfate to dehydroepiandrosterone, a weak androgen, which can be converted to the biologically active androgens testosterone and 5α-dihydrotestosterone by other steroidogenic enzymes also present in skin. A number of potent, irreversible STS inhibitors have been developed based around a core arylsulfamate ester motif, the active pharmacophore required for potent STS inhibition. Such inhibitors include AHBS and STX-64. Topical application of AHBS to the skin of mice or pigs resulted in almost complete inhibition of skin STS activity. Furthermore, when applied to the skin of Göttingen minipigs daily for 2 weeks, by day 10 AHBS had inhibited sebum production, a desired requisite for an anti-acne drug. When applied topically to the skin of nude mice at 1.0 and 10.0 mg/kg STX-64 inhibited skin STS activity by > 90%, but it also inhibited liver STS activity. While preclinical studies have confirmed the ability of topically applied STS inhibitors to inhibit skin STS activity, further studies using preclinical models of skin disorders and clinical trials are needed to test their efficacy in treating skin disorders.

Introduction

Inhibition of steroid sulfatase (STS) activity represents a novel target for the treatment of a number of skin disorders. STS regulates the hydrolysis of steroid sulfates such as dehydroepiandrosterone sulfate (DHEAS) and estrone sulfate (E1S) to dehydroepiandrosterone (DHEA) or estrone (E1), respectively. DHEA and E1 can be converted to more active androgens (testosterone, 5α-dihydrotestosterone [5α-DHT]) or estrogens (estradiol [E2]). Considerable research has been carried out over the last decade to develop STS inhibitors (1-4). So far, attention has focused on using STS inhibitors for the treatment of hormone-dependent cancers. STX-64 (also known as 667-COUMATE or BN-83495) has completed a phase I trial for the treatment of postmenopausal women with advanced hormone-dependent metastatic breast cancer (5, 6).

In addition to their use for hormone-dependent cancer therapy, STS inhibitors could also have considerable therapeutic potential for the treatment of a number of skin disorders. Such conditions include hirsutism, androgen-dependent alopecia (AGA), acne, excess sebum production and psoriasis. A combination of an STS inhibitor with minoxidil may also be useful in the treatment of AGA. It is also possible that STS inhibitors could be included in deodorant formulations. With the advent of potent STS inhibitors, a limited number of preclinical studies have been carried out to test the efficacy of some inhibitors when applied topically to the skin of rodents or pigs. The encouraging results obtained from these studies suggest that it should be possible to develop STS inhibitor-containing formulations that can be applied topically. It is therefore timely to review the potential use of STS inhibitors for the topical treatment of skin disorders.

STS and androgen synthesis in skin

STS (EC 3.1.6.2, arylsulfatase C) is the enzyme responsible for the hydrolysis of alkyl (*e.g.*, DHEAS) and aryl steroid sulfates (*e.g.*, E1S) to their unconjugated

form. STS activity was first demonstrated in rat liver microsomes more than 50 years ago (7) and is now known to be ubiquitously distributed throughout the body and to be present in skin and its appendages (2, 8). STS is only the first enzyme required for the cascade that converts inactive DHEAS to the biologically active androgens testosterone and 5α-DHT (Fig. 1). Other enzymes required for this biotransformation include the Δ^{5-4} isomerase/3β-hydroxysteroid dehydrogenase to convert DHEA to androstenedione, 17β-hydroxysteroid dehydrogenase types 3 and 5 to convert androstenedione to testosterone and 5α-reductase to transform testosterone to 5α-DHT. All these enzymes and the androgen receptor (AR) are present in skin (9-11). Thus, inhibition of STS, which acts on DHEAS, the main precursor for the synthesis of biologically active androgens in skin, is an attractive therapeutic target for inhibition.

STS inhibitors

The first specifically designed and synthesized STS inhibitor was estrone methylthiophosphonate, an E1S surrogate, which possessed modest STS-inhibitory properties (12, 13). Extensive structure–activity relationship studies led to the identification of estrone-3-*O*-sulfamate (EMATE, **1** in Fig. 2) as the first potent STS inhibitor (14).

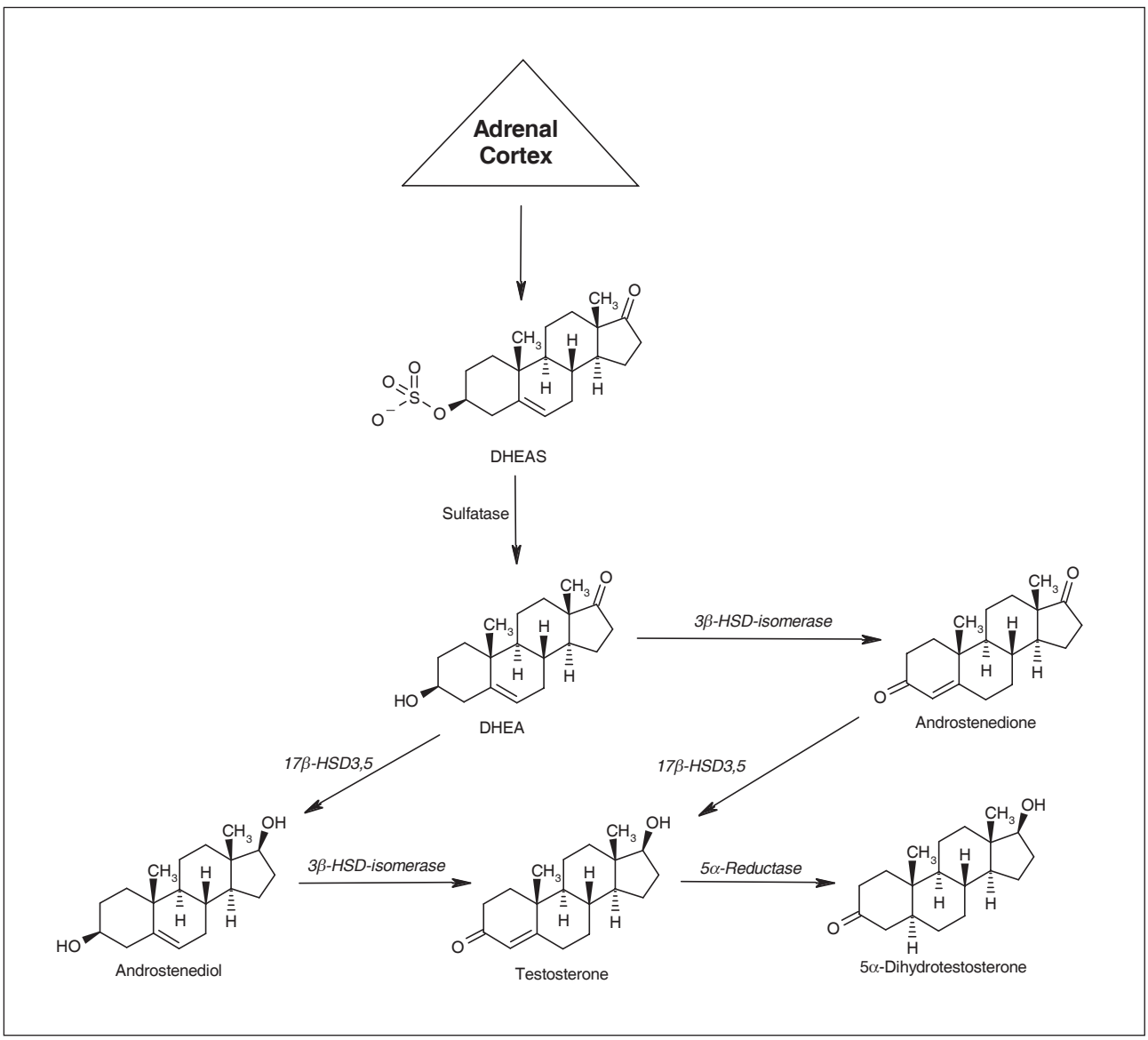

Fig. 1. Pathway for the synthesis of biologically active androgens in skin. Dehydroepiandrosterone sulfate (DHEAS) can be hydrolyzed to dehydroepiandrosterone (DHEA) by the action of steroid sulfatase (STS) in peripheral tissues including skin. Other steroidogenic enzymes are also present in skin: 3β-hydroxysteroid dehydrogenase-Δ^{5-4} isomerase (3β-HSD-isomerase) converts DHEA to androstenedione, which is then converted to testosterone; 17β-hydroxysteroid dehydrogenases type 3 and 5 (17β-HSD3,5) converts DHEA to androstenediol, which is then converted to testosterone; and 5α-reductase reduces testosterone to 5α-dihydrotestosterone.

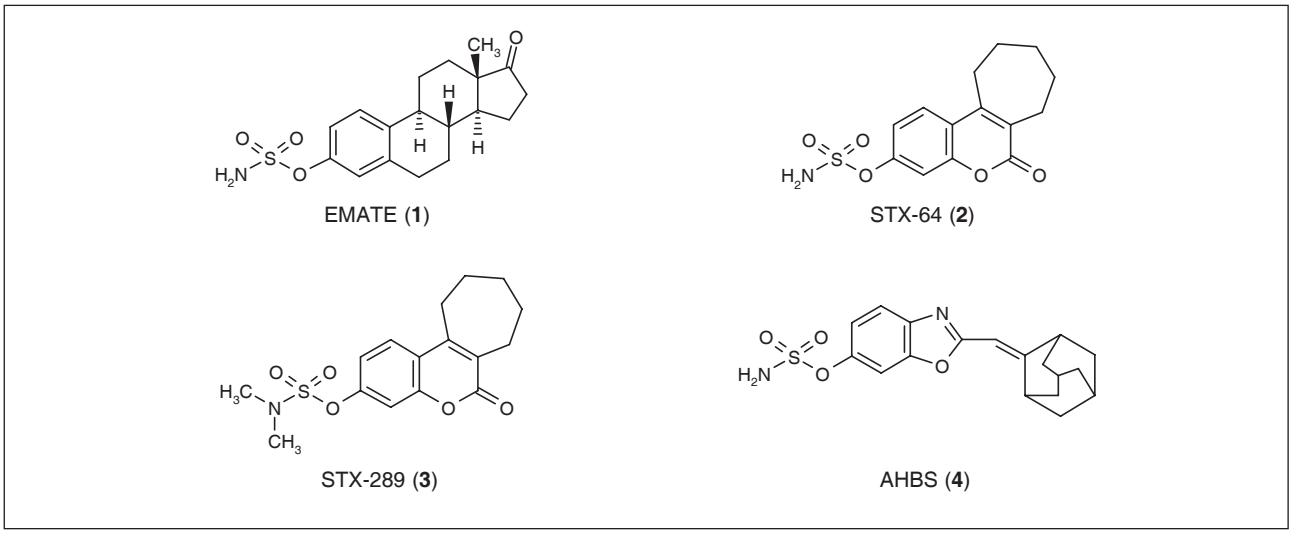

Fig. 2. Chemical structures of selected steroid sulfatase (STS) inhibitors. **1**, Estrone-3-*O*-sulfamate (EMATE); **2**, STX-64; **3**, STX-289; **4**, 6-[2-(adamantylidene)hydroxybenzoxazole]-*O*-sulfamate (AHBS).

EMATE was shown to inhibit STS activity in placental microsomes and MCF7 breast cancer cells in an irreversible manner (15). When administered orally to rats, it proved to be active *in vivo* in inhibiting the hydrolysis of both E1S and DHEAS. Furthermore, it inhibited the growth of E1S-stimulated nitrosomethylurea-induced mammary tumors in ovariectomized rats (16). Unexpectedly, however, the estradiol derivative of EMATE was found to have potent estrogenic properties, being 5 times more estrogenic than ethinylestradiol in rodents on oral application (17). While EMATE was therefore considered unsuitable for development as a therapy for women with breast cancer, it could, as will be discussed later, have potential for use as a topical STS inhibitor.

In order to reduce the estrogenicity associated with EMATE, a number of 2- and 3-ring steroid mimetics were designed, synthesized and tested. This research led to the identification of STX-64 (**2** in Fig. 2), a tricyclic coumarin sulfamate (18, 19), and its *N,N*-dimethyl analogue STX-289 (**3** in Fig. 2) While STX-289 is inactive *in vitro*, it undergoes demethylation *in vivo* to become a potent STS inhibitor (20). STX-64 was shown to be devoid of estrogenic activity, as tested in an ovariectomized rat uterotrophic assay (21). Many other STS inhibitors have now been identified, including 6-[2-(adamantylidene)hydroxybenzoxazole]-*O*-sulfamate (AHBS, **4** in Fig. 2) (22). However, to date, all highly active and irreversible STS inhibitors incorporate the phenol sulfamate ester pharmacophore required for potent STS inhibition (18).

Skin conditions potentially amenable to topical STS inhibitor therapy

Skin comprises the largest organ in the body and there is increasing evidence that STS in skin and its appendages makes an important contribution to androgen production. In addition, STS may also play a role in the regulation of T helper (Th) cell maturation (23-25), which may be involved in chronic proliferative disorders such as psoriasis. Skin contains several androgen-sensitive appendages, including hair follicles, sebaceous glands and sweat glands. The importance of STS in skin function has been known for some time since its deficiency in X-linked ichthyosis was established (26, 27). A deficiency in STS manifests itself in skin by causing scaling. The presence of STS, and other steroidogenic enzymes which can convert DHEA to testosterone and 5α-DHT, has focused attention on the role that STS may have in a number of skin disorders.

Hirsutism

Human skin is a target tissue for sex steroids and androgens play a major role in the pathogenesis of hair disorders such as hirsutism (11, 28). Hyperandrogenism is primarily a disorder of females and can be associated with a number of conditions, including polycystic ovary syndrome (PCOS), which has a prevalence of 6-10% in women of childbearing age (29, 30). While the origin of excess androgen production in women with conditions such as PCOS remains controversial, it is likely that increased production of DHEAS, and its subsequent uptake and activation in skin, could contribute to the hirsutism associated with this condition. Circulating DHEAS concentrations are increased in a significant proportion of women with hirsutism (31, 32). While virilizing tumors of the adrenal gland or ovary can also give rise to hirsutism, such conditions would not be amenable to topical STS inhibitor therapy.

The pioneering studies of Hoffmann and colleagues first suggested that inhibition of STS could be of potential therapeutic value in the treatment of androgen-dependent

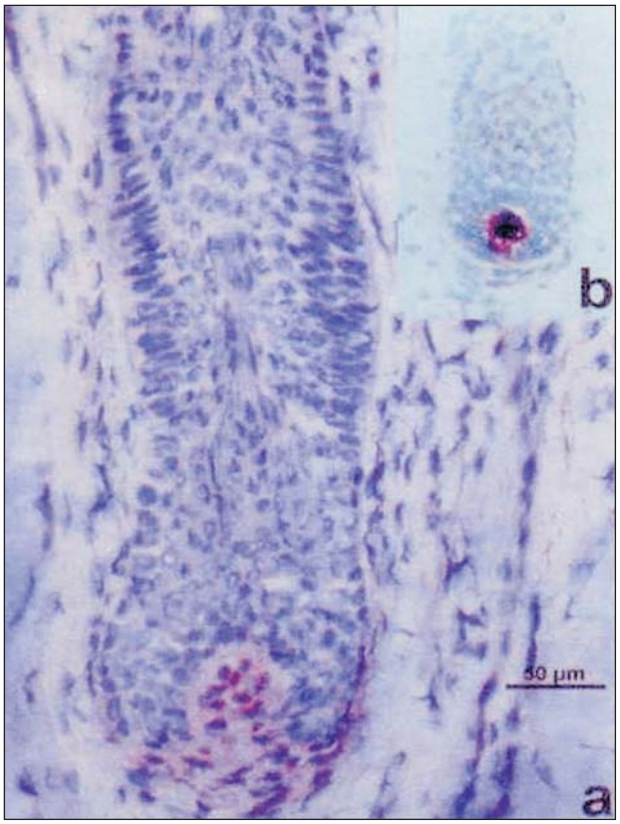

Fig. 3. Localization of steroid sulfatase (STS) in human hair follicle. (**a**) Using a specific anti-STS antibody, the enzyme (red stain) was found to be almost exclusively located in hair follicles, with cells of the dermal papilla showing strong STS immunoreactivity. (**b**) Dermal papilla in velus hair follicles also showed strong immunoreactivity. Reproduced with permission from Hoffmann *et al.* (28).

skin disorders (33). It has been known for many years that DHEAS can be converted to 5α-DHT in hair follicles (34). Hoffmann's group demonstrated that the highest level of STS immunoreactivity and activity was located in the dermal papilla of the hair follicle (Fig. 3). Importantly, this is the part of the hair follicle where 5α-reductase type 2 and the AR are located (35, 36). Thus, all the machinery is contained within the hair follicle to convert DHEAS to the biologically active androgens testosterone and 5α-DHT. Hoffmann also demonstrated that the STS inhibitor EMATE, even at concentrations as low as 1 nM, could efficiently block STS activity in different hair follicle fractions (33). The ability to inhibit STS activity in hair follicles clearly suggests the development of topical STS inhibitors to block the activation of DHEAS in skin for use in conditions such as hirsutism.

AGA and potentiation of topical minoxidil therapy

Elevated serum concentrations of DHEAS have also been implicated in AGA, the hereditary thinning of hair in genetically susceptible individuals (37, 38). While it has been proposed that an STS inhibitor could be used to treat this condition (33), the use of such an inhibitor in combination with minoxidil, an approved therapy for this condition, would seem worthy of further exploration. Minoxidil was introduced in the 1970s for the treatment of hypertension, and hypertrichosis was observed as a common side effect in those taking this medication (39). This unexpected finding led to the development of a topical formulation for the treatment of AGA in men and subsequently in women. When used to treat AGA, minoxidil must be applied topically twice daily to achieve and maintain efficacy (40).

Despite much research carried out over the last two decades, it is still not clear by what mechanism minoxidil stimulates hair growth (39). Possible mechanisms include a direct effect on hair growth or an indirect effect from the vasodilatation and increased blood flow that result from this therapy. Minoxidil is able to induce a rapid relaxation of vascular smooth muscle due to its ability to cause opening of plasma membrane ATP-sensitive potassium channels (41, 42). Importantly for this review, studies by Buhl and colleagues showed that the drug acts only in its sulfate form to cause relaxation of vascular smooth muscle, and also in its effects on hair follicles (43). Minoxidil sulfate was more potent than the parent compound in stimulating mouse vibrissae hair follicles, and drugs that blocked the formation of minoxidil sulfate also blocked the activity of the parent compound, but not of the sulfated metabolite (43). Thus, minoxidil sulfate, in contrast to all steroid sulfates which are biologically inactive, requires sulfation to exert its effects.

A number of phenol sulfotransferases for the sulfation of minoxidil have been characterized and there is biochemical evidence for minoxidil sulfation by two phenol sulfotransferases in hair scalp (44). While minoxidil sulfate can therefore be formed by phenol sulfotransferase in some tissues, further research is required to confirm whether it can act as a substrate for STS. In view of its structure, however, it is possible that it will be a substrate for STS, and thus STS inhibition could potentiate its action *in vivo*.

Minoxidil sulfate itself has not been incorporated into any topical formulations, as the sulfate derivative is very unstable in aqueous solution and is rapidly hydrolyzed to the parent drug (45). As minoxidil is only active as its sulfate metabolite, its combination with an STS inhibitor in a topical formulation should be evaluated for the treatment of AGA in men and women. Thus, the STS inhibitor would not only inhibit the hydrolysis of DHEAS in skin and reduce the formation of active androgens, but could also potentiate the effects of minoxidil by preventing the enzyme-catalyzed hydrolysis of the sulfate metabolite after its formation in skin or hair follicles. If such a combination should prove to be effective, it may reduce the frequency required for the topical application of minoxidil.

Acne and seborrhea

Acne vulgaris is a common skin disorder affecting 60-70% of adolescents and young adults, but which also fre-

quently occurs in women aged over 25 years (46). Seborrhea results in an increase in the rate of sebum production and is considered to be a precursor to the development of acne. The increase in androgen levels that occurs at adrenarche and/or menarche can result in enlargement of the sebaceous gland and an increase in sebum production. This can result in blockage of the pilosebaceous duct, leading to the development of micromedo, the characteristic acne lesion. Subsequent colonization of the blocked sebaceous gland by the anaerobic bacterium *Propionibacterium acnes* can result in the gland becoming inflamed.

The development of acne in prepubertal children has been related to the rise in serum DHEAS concentrations which occurs at this time (47, 48). DHEAS is also considered to be an important regulator of sebum production (49, 50). DHEAS is biologically inactive, but as discussed previously, all the enzymes required for its conversion to potent androgens are present in skin, including the sebaceous gland. DHEAS is present at high concentrations in the circulation, but relatively high levels have also been detected in skin (51).

While androgens such as testosterone can be taken up from the circulation, the local synthesis of testosterone in the skin and sebaceous gland is thought to make an important contribution to its production. Although STS is present in skin, an initial study found no difference in STS activity in epidermis taken from acne-prone and non-acne-prone skin (52). In a more recent study, an antibody against STS was used to carry out an immunohistochemical examination of acne skin (53). Strong STS immunoreactivity was observed in skin with acne lesions but not in unaffected skin areas. Importantly, results from this study showed that in acne lesions most STS immunoreactivity was associated with leukocytes infiltrating the lesions. In related *in vitro* experiments, activation of monocytes by bacterial products led to a marked increase of STS immunoreactivity and activity. It has previously been shown that cytokines, such as tumor necrosis factor α (TNF-α) and IL-6, can enhance STS activity in MCF7 breast cancer cells (54). It is therefore likely that infiltrating monocytes release cytokines, which are able to stimulate STS activity within these cells in areas of skin with acne lesions.

Current therapies for the treatment of acne include antibiotics, topical or systemic retinoids or therapies to reduce or block androgen action (46, 55). In women with moderate or severe acne, oral contraceptive therapy is frequently employed (56). This acts to inhibit gonadotropin secretion, which reduces androgen production by the ovaries and adrenal glands. In addition, the estrogenic component stimulates sex hormone-binding globulin (SHBG) production, which binds testosterone with high affinity and reduces the level of biologically available free testosterone. Systemic antiandrogens such as cyproterone acetate are also used to treat acne in female patients but can not be used for male patients. The topical nonsteroidal antiandrogen inocterone was shown to produce a small but significant reduction in the number of acne lesions in a 12-week trial, but did not reduce the comedo count or sebum excretion rates (57). It may also be possible to use inhibitors of 5α-reductase type 1, which is present in skin, to treat acne, but so far there is no convincing evidence that such therapy is effective for the treatment of this skin disorder.

As acne is such a common skin condition, there is an urgent need to develop new, preferably topical, treatments. Androgen depletion, inhibition of androgen metabolism or blocking androgen action have so far proved to be only partially effective for the treatment of acne (50). Furthermore, as such therapies have to be administered systemically to be effective, there is a risk of adverse events occurring in an otherwise healthy population. Thus, the development of an effective topical STS inhibitor could offer considerable potential for the treatment of acne.

Psoriasis

While it is now acknowledged that skin is an important site for steroid sex hormone synthesis and metabolism, there is a growing interest in the role that the immune system may have in regulating several aspects of skin function (58-60). Psoriasis is a chronic inflammatory skin disease that is estimated to affect 1-3% of the world's population (61). The disease is characterized by hyperproliferation of keratinocytes in association with abnormal epidermal differentiation, now recognized to be a reaction to the immune system in focal skin regions (62). Aberrant infiltration of Th type 1 (Th1) cells occurs together with macrophages and neutrophils (61). Psoriasis is now considered to be the most prevalent T cell-mediated inflammatory disorder in humans (63).

STS in macrophages in lymphoid tissue is thought to have a crucial role in the maturation of Th cells to either a Th1 or Th2 phenotype (23, 24). Th1 and Th2 cells each secrete a different profile of cytokines (*e.g.,* Th1 cells secrete IL-2 and interferon gamma [IFN-γ]; Th2 cells secrete IL-6 and IL-10). The response of Th cells is mutually exclusive, with IFN-γ inhibiting the formation of Th2 cells and IL-10 inhibiting the formation of Th1 cells (25). From such investigations, it has emerged that the ratio of the adrenal androgen DHEA to the adrenal glucocorticoid cortisol determines whether cells progress to either a Th1 or Th2 phenotype, *i.e.,* DHEA favors the development of Th1 cells, whereas cortisol promotes a Th2 response. Thus, the crucial role of STS within lymphoid tissue is to control the formation of DHEA from DHEAS and regulate the DHEA to cortisol balance.

As STS is present in skin and also in infiltrating macrophages, it is possible that it could have a similar immunomodulatory role to that which occurs in lymphoid tissue. Inhibition of STS in skin could therefore promote a glucocorticoid environment favoring a Th2 response and inhibiting the production of Th1-type cytokines which are implicated in the pathogenesis of psoriasis (61). By inhibiting the production of Th1-type cytokines, a topical STS inhibitor could therefore have therapeutic potential for the treatment of psoriasis.

As discussed previously, STS deficiency blocks the hydrolysis of cholesterol sulfate, resulting in ichthyosis. Application of cholesterol sulfate to the skin of nude mice can cause epidermal hyperkeratinization (64). As an STS inhibitor would also block the hydrolysis of cholesterol sulfate, the need for caution in the use of topical inhibitors for the treatment of psoriasis has been raised (61). While such a possibility will have to be fully investigated in clinical trials, no thickening of the stratum corneum was detected when an STS inhibitor was topically applied in a preclinical model (22).

Steroidal malodor

Androgens are also implicated in the production of axillary steroidal malodor. The use of an STS inhibitor as part of a deodorant preparation has been proposed to counter this disorder (65). Androgens can promote perspiration, as males sweat at a greater rate than females (66, 67). However, the effect of androgens on perspiration rates is indirect, as androgen or antiandrogen therapy has not been found to alter perspiration rates (66).

The axillary apocrine gland produces a secretion that is a complex mixture containing cholesterol, steroids and other lipids, and it is from this excretion that axillary malodor is generated (65). The sterile secretion, which contains androgen conjugates, is odorless. Androgen conjugates in this fluid include the sulfates and glucuronides of 5α-androstenol and 5α-androstenone. These conjugates are subjected to hydrolysis by bacterial exoenzymes and the resulting free steroids account for a proportion of axillary malodor. Zinc glycinate was found to inhibit the activities of the bacterial enzymes and could therefore have potential for incorporation into a deodorant formulation. With the discovery of more potent, topically active STS inhibitors, their use in such preparations warrants further investigations.

Pharmacology and stability of STS inhibitors

All STS inhibitors based on the phenol sulfamate ester structure exhibit prolonged *in vivo* inhibition of STS activity (16, 68). These compounds act as irreversible inhibitors of STS activity, and once inhibited, new protein has to be synthesized for restoration of activity to occur. After oral application and absorption, sulfamate-based inhibitors are transported into red blood cells by binding to carbonic anhydrase II, and transit the liver without undergoing first-pass inactivation (20, 69). *In vivo* after oral or intravenous administration to rats, both STX-64 and AHBS were very stable, with only low levels of the corresponding phenol (*i.e.,* desulfamoylated) metabolites being detected (22, 70).

Previous studies have indicated that at neutral pH, desulfamoylation of STX-64 and related inhibitors can occur (71). The *N,N*-dimethyl analogue STX-289 was therefore synthesized and evaluated, as it was thought that this compound would be more robust and could act as a prodrug for the formation of STX-64 via demethylation *in vivo,* and might, as a more hydrophobic entity ($c_{log}P$: 2.29, cf. 1.73 for STX-64) (72), also be suitable for topical application. However, in rodents and humans, these sulfamate-based STS inhibitors appear to be resistant to desulfamoylation, endowing them with a prolonged duration of action (5, 22, 70).

Preclinical models of topical STS inhibition

Since the discovery of potent sulfamate-based STS inhibitors, many studies have confirmed their *in vivo* efficacy (reviewed in Ref. 2). In rodents, oral dosing with EMATE or STX-64 at 10 mg/kg resulted in almost complete and prolonged inhibition of STS in liver and body tissues (16, 21).

Two preclinical studies have been carried out to investigate the ability of topically applied sulfamate-based compounds to inhibit STS activity. Billich and colleagues carried out a series of investigations to examine the ability of AHBS to inhibit skin STS (22). When applied topically to the back skin of mice in an ethanolic solution at a concentration equivalent to 10 mM, AHBS resulted in > 99% inhibition of skin STS activity. As rodent skin is more permeable than human skin, they also applied AHBS to the skin of pigs, which is considered to be a more appropriate model for human skin with regards to drug permeation (73). Again, topical application of 1% and 3% ethanolic solutions of AHBS resulted in almost complete blockade of skin STS. The epidermis plus stratum corneum layer from human cadavers was used to examine if AHBS penetrated human skin. After epicutaneous application as a 1% solution in either ethanolic or isopropane:propylene glycol (1:1), high concentrations of AHBS (130-190 μg/g) were detected in human skin. AHBS was also shown to inhibit STS activity in the dermal compartment of human skin, giving 90% inhibition when applied as a 1% solution.

The potential for inducing ichthyosis-like changes in skin was investigated by applying AHBS topically to the backs of Göttingen minipigs. The dose was applied daily for a 2-week period. Histological examination of the test sites did not reveal any increased thickening of the stratum corneum. This finding led the investigators to conclude that only prolonged absence of STS will lead to the accumulation of cholesterol sulfate in blood and its deposition in skin. Another important finding from this study in minipigs was that the treated area examined on day 10 of the study did not become discolored, in contrast to the nontreated area (Fig. 4). This suggests that the compound is antiseborrheic, the exact property that is required for a drug for the treatment of acne.

In the second study, Purohit and colleagues examined the ability of STX-64 and a related analogue, STX-289, to inhibit skin STS activity in a nude mouse model (74). Oral administration of both compounds at 1 and 10 mg/kg resulted in almost complete inhibition of skin and liver STS. When applied topically to the neck region of nude mice at 1 or 10 mg/kg in tetrahydrofuran, not only skin but, unexpectedly, also liver STS activity was effec-

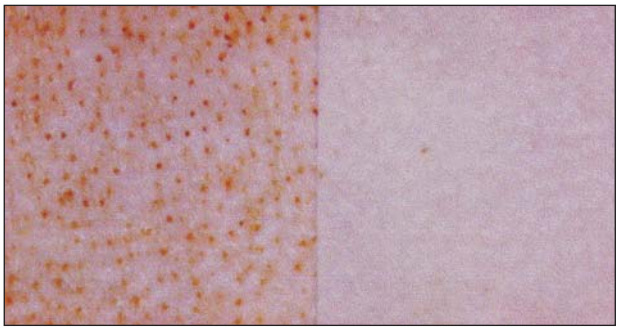

Fig. 4. Effect of topical application of 6-[2-(adamantylidene)hydroxybenzoxazole]-*O*-sulfamate (AHBS) to the backs of Göttingen minipigs. Photographs taken on day 10 after daily dosing showing: left panel, vehicle-treated site; right panel, AHBS-treated site. As can be clearly seen, the normal perifollicular discoloration observed at the vehicle-treated site caused by sebum production did not occur in AHBS-treated animals due to the lack of sebum production. Reproduced with permission from Billich *et al.* (22).

tively inhibited (Fig. 5). The *N,N*-dimethyl analogue of STX-64, STX-289, which may be more suitable for topical formulation, also effectively inhibited skin and liver STS when applied topically. This finding suggests that STX-289 is either demethylated in skin or, alternatively, after absorption, when it can then act systemically to inhibit skin and liver STS. As it may not be desirable for liver STS to be inhibited as a result of topical application of an STS inhibitor, it may be necessary to modify their structures so that they are preferentially localized in the skin, thus minimizing systemic exposure.

Summary

It will be apparent from this review that topically applied STS inhibitors could have a major impact on the treatment of a number of skin disorders. The sulfamate-based STS inhibitors STX-64 and AHBS have been shown to inhibit skin STS when applied topically. Application of AHBS to the skin of minipigs produced convincing evidence that this resulted in inhibition of sebum production. STX-64 when applied topically not only inhibited STS in the skin of nude mice, but was readily absorbed and exerted a systemic effect, inhibiting liver STS activity in treated animals. Thus, drugs such as STX-64, in a formulation for topical application, could exert a 2-fold effect on skin conditions. Firstly, by direct inhibition of skin STS, blocking the hydrolysis of DHEAS delivered to the skin from the blood, and secondly, a systemic effect on the liver and other tissues to reduce levels of weak androgens such as DHEA and androstenedione, which are available for uptake by skin. In the phase I trial of STX-64 in postmenopausal women with breast cancer, serum concentrations of androstenedione and testosterone were found to significantly decrease as a result of STS inhibition (5). This indicates that, at least in postmenopausal women, androstenedione is derived from the peripheral conversion of DHEAS and not, as previously

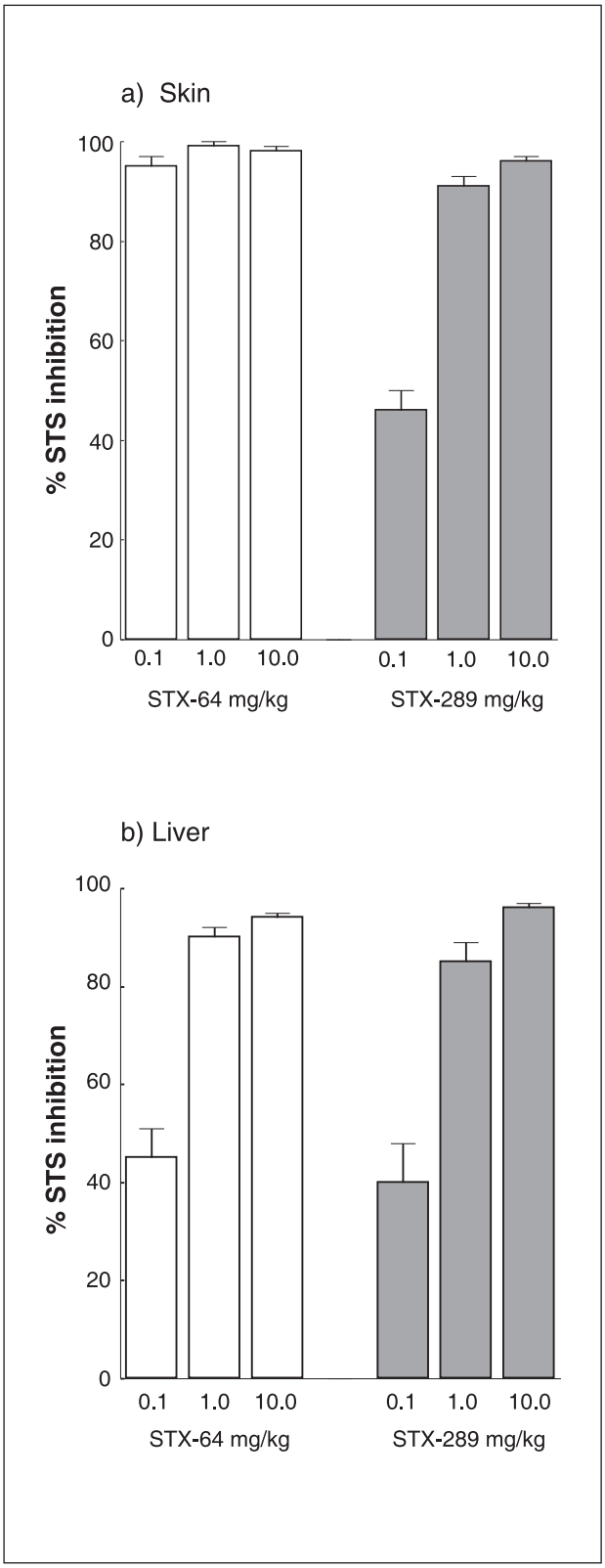

Fig. 5. Inhibition of skin (**a**) and liver (**b**) steroid sulfatase (STS) activity after the topical application of STX-64 or STX-289 to the skin of nude mice. When applied at 1 and 10 mg/kg, STS activity in skin and liver was almost completely blocked by both compounds. Reproduced with permission from Purohit *et al.* (74).

thought, by direct secretion from the adrenal cortex. This finding therefore lends support to the concept of inhibiting skin STS to reduce levels of biologically active androgens.

Topical application of STS inhibitors could also have the potential to be used in the longer term preventive setting for conditions such as mild hirsutism, acne and AGA. In AGA, an STS inhibitor could be applied in combination with minoxidil to potentiate the action of this drug on hair growth. Most current therapies used for skin disorders have to be applied systemically, increasing the risk of adverse events occurring in an otherwise generally young, healthy population. Thus, the development of topically applied therapies could reduce the risk of adverse events.

While STX-64 and AHBS are devoid of estrogenicity, it is possible that an STS inhibitor with estrogenic properties (arising from the removal of the sulfamoyl group), such as EMATE (11), could have a role in the treatment of some skin conditions in women. Estrogens inhibit sebum production (49, 56) and can have beneficial effects on skin, particularly in postmenopausal women (75-77). Thus, an STS inhibitor with some associated estrogenicity might be of therapeutic value for the treatment of acne in women. It would be important to ensure that the use of a potentially estrogenic STS inhibitor, such as EMATE, does not increase the exposure of breast tissues to estrogen. As conditions such as psoriasis tend to regress during pregnancy, estrogens may exert beneficial effects on the progression of this disorder (78, 79). It would therefore seem worthwhile to explore the potential of the topical use of EMATE for the treatment of psoriasis.

Given the potency of this new class of sulfamate-based STS inhibitors, it will be important to carry out clinical trials to assess the feasibility of using them topically. Trials of topically applied STS inhibitors should be carried out in patients with mild hirsutism, acne and chronic proliferative skin disorders such as psoriasis. In addition, the combination of an STS inhibitor with minoxidil should be explored for the treatment of AGA in men and women. As most current therapies for these conditions are not fully successful, the development of topical STS inhibitors offers hope for a novel treatment option for conditions which, while not life-threatening, can affect a large number of men and women for prolonged periods of their lives.

Disclosure

Professors Reed and Potter are Directors of Sterix, Ltd. Professors Reed and Potter and Dr. Purohit act as consultants to Ipsen, Ltd. This research was supported by Sterix, Ltd., a member of the Ipsen Group.

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