

Original Article

Phase I and Phase II clinical trials of androst-5-ene-3 β ,7 β ,17 β -triol

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Abstract: The immune regulating DHEA metabolite, androst-5-ene-3 β ,7 β ,17 β -triol (β AET), was evaluated for safety, cholesterol lowering, and vaccine enhancement in phase I and phase II clinical trials. Safety and pharmacokinetics were evaluated in one study of normal subjects that received β AET or placebo transmucosally (buccal tablets) for 4 days. In a second study β AET was given by daily subcutaneous injection for 3 days. β AET was subsequently evaluated in placebo-controlled trials for cholesterol lowering in hyperlipidemic subjects and for potentiation of hepatitis B surface antigen (HBsAg) vaccine in elderly subjects. Adverse events were primarily associated with injection site reactions. Pharmacokinetics indicated that β AET was rapidly cleared after either route of administration in both normal and elderly subjects. Plasma β AET concentrations typically declined below the limit of detection within a few hours of administration. β AET pharmacokinetics was similar in males and females and in normal and elderly subjects. β AET significantly lowered cholesterol in normal adult, but not in elderly or hyperlipidemic subjects. HBsAg titers were not increased in elderly β AET treated subjects relative to placebo. Conclusions: Short-term administration of β AET is safe in humans. β AET has a cholesterol lowering effect in healthy humans, but not hyperlipidemics. Exogenous β AET appeared to be rapidly metabolized, which may be consequential to the lack of pharmacological activity. A longer duration of β AET treatment with higher doses or chemical derivatives that are resistant to metabolic inactivation are likely necessary to treat human disease. The utility of β AET in humans may be limited to maintenance of homeostasis in healthy adults.

Keywords: Androstenetriol, safety, pharmacokinetics, β AET

Introduction

Numerous experiments with exogenous dehydroepiandrosterone (DHEA) have demonstrated diverse beneficial effects in rodents, including attenuation of the aging phenotype, and decreases in inflammation, obesity and carcinogenesis [1]. In rodents DHEA has remarkable anti-inflammatory properties without being immune suppressive, restores immune competence [2] and opposes certain untoward effects of glucocorticoids [3]. However, activity in humans has been difficult to substantiate. The species dependency may be attributed to mechanistic factors [4], bioavailability [5] and differential metabolism [6]. Recent publications have demonstrated that at least some of the anti-inflammatory activity of DHEA is shared by, or can be attributed to, its di-, tri-, and tetra-hydroxylated metabolites, such as androst-5-ene-3 β ,7 β ,17 β -triol (β AET) [7-9].

In vitro metabolism studies and β AET pharmacokinetics indicate that β AET (like DHEA) is rapidly metabolized by both rodents and primates [10]. Transmucosal (buccal) administration of β AET to cynomolgus monkeys yields predominantly glucuronide and sulfate conjugates of 3 β ,7 β -diol-androst-5-en-17-one, 3 β ,7 α -dihydroxy-androst-5-en-17-one, 3 β -hydroxy-androst-5-en-7,17-dione in blood and urine, in addition to low levels of these metabolites and parent β AET as free steroids [10]. β AET is naturally present in human plasma at concentrations ranging from 2-250 pg/mL [11], in addition to approximately 700 pg/mL of 7 α / β -hydroxy-DHEA [12]. Reductase forms of the enzyme 17 β -hydroxysteroid dehydrogenase (17 β -HSD) catalyze the conversion of DHEA to androst-5-ene-3 β ,17 β -diol (5-AED) [13], which is approximately 10 nM in human plasma [14]. The sequence of C-7 and C-17 enzymatic reactions that lead to β AET formation are inter-

changeable and androstene C-7 hydroxylation dynamics have been described elsewhere [15, 16].

β AET does not bind or transactivate androgen (AR), estrogen (ER α), glucocorticoid [10], or PPAR nuclear receptors [4]. Importantly, β AET cannot be metabolized into sex steroids [17], but retains immune regulatory properties [18, 19]. *In vitro* β AET opposed glucocorticoid-induced anti-proliferative and cytokine-suppressive effects in macrophages and splenocytes [20, 21] and has potent anti-inflammatory and immune modulation properties in various animal models of inflammation [18, 19, 22]. Because many of the key activities attributed to DHEA may reside in β AET, this compound was developed with the intent of translating DHEA's immune modulating activity into humans. Because androstenes have poor oral bioavailability [5], alternative routes of administration, subcutaneous and transmucosal, were chosen to ensure that the agent was introduced into systemic circulation. Nonclinical subcutaneous toxicology studies (28 days) in rats and monkeys produced no adverse pharmacological effects [10], nor did buccal tablets produce irritation in hamsters. This report describes our exploratory clinical experience in placebo controlled Phase I trials in normal healthy individuals. An unexpected lipid lowering observation prompted a Phase II trial that was designed to explore the effects of β AET in hyperlipidemic subjects. In addition β AET increased antibody responses to protein immunogens in aged mice [10], which lead us to a placebo controlled Phase II study using subcutaneous β AET concurrently administered with primary and secondary HBsAg vaccinations in an elderly population. We describe the results of the Phase I and Phase II studies with β AET.

Methods

Test product

β AET [23] (CAS 2697-85-0, Niels Clauson-Kaas Chemical Research Laboratory, Farum, Denmark) was micronized (Micron Technologies, Exton, PA) and formulated for subcutaneous injection as a 100 mg/mL isotonic sterile aqueous suspension, pH 7.4 (University of Tennessee Department of Pharmaceutical Sciences, Memphis, TN), and placebo was a solution of the same composition, without β AET. β AET was also formulated in a 25 mg potency tablet for

transmucosal administration. Placebo tablets were of the same size and composition without the active ingredient.

Pharmacokinetics

Plasma samples for pharmacokinetic (PK) measurements were analyzed for β AET by LC-MS/MS compliant with GLP. The quantifiable range for the assay was 5.0-2,500 ng/mL. [The upper range of endogenous β AET concentrations in plasma is 0.2 ng/mL [10].]

Plasma samples with concentrations below the quantifiable limit (5.0 ng/mL, BQL) were excluded from PK parameter calculations, noting that a high frequency of BQL values hindered calculations of the integrated exposure and elimination constant. Values for the maximum concentration (C_{max}) are reported as observed.

Clinical studies

The studies were approved by the Institutional Review Boards (IRB) of the participating clinical sites and performed in accordance with the guidelines of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice provisions of the Medical Research Involving Human Subjects Act and the Declaration of Helsinki. All subjects/patients provided written informed consent prior to participating in the studies. (The β AET doses used in humans were approximated as body surface equivalent to pharmacologically active doses in murine models of inflammatory disease.)

Phase I studies

Healthy adult and elderly subjects were randomized (3:1 active to placebo) to receive three consecutive daily subcutaneous injections of placebo, 50 or 100 mg β AET, followed by 2 months of periodic observation (trial HE2200-100), or to receive placebo, 25 or 100 mg β AET transmucosally (buccal administration) once daily for five days followed by 2 months of periodic observation (trial HE2200-101). Subjects were stratified into two groups based on age: 18 to 50 years inclusive or 65 to 85 years inclusive. In order to clearly distinguish potential age related pharmacological effects, subjects between age 51-64 were ineligible for the study. Treatment of the elderly cohorts was initiated after confirming the absence of severe adverse reactions in the adult cohort.

After consent, subjects were screened [medical and psychiatric history, physical examination (PE), electrocardiogram (ECG), vitals signs including height and weight, clinical laboratory testing (Northwest Kinetics, Tacoma, WA) including hematology, chemistry, lipid profile, urinalysis, G6PDH, estradiol and testosterone] for eligibility into the study. In-patient procedures included drug administration, evaluation of injection site reactions, PE, ECG, vital signs, clinical laboratory testing, and collection of blood samples for immunological (Hematologics, Inc. Seattle, WA) and pharmacokinetic analyses. Vital signs, adverse events, and concomitant medications were monitored during follow-up visits.

Phase II study HE2200-120

Healthy hepatitis B-naïve, elderly (65-85 years old) volunteers, who qualified and consented to receive hepatitis B vaccine (Recombivax HB®) were randomized (1:1) to concomitantly receive either 100 mg of β AET or placebo equivalent. Subjects received 3 once daily subcutaneous injections of study drug or placebo prior to the first and second dose of hepatitis B vaccine given 28 days apart. The third dose of vaccine was given at 6 months without β AET treatment with study termination 28 days later. Antibody titers against HBsAg were measured (UC Davis, Sacramento, CA) 28 and 32 days after the first vaccination and approximately 28 days after the second and third vaccinations. Hematology and clinical chemistry values were monitored for safety (Mayo Clinical Trial Services, Rochester, MN).

Phase II study HE2200-130

Dyslipidemic subjects, ages 18-70 years, with plasma triglyceride concentrations 150-800 mg/dL, total cholesterol levels of 220-320 mg/dL and HDL levels of \leq 45 mg/dL for males and \leq 55 mg/dL for females were eligible to participate in the study. After informed consent was obtained, subjects initiated a Step II AHA diet and discontinued all lipid-lowering agents for a six-week run-in period. Evaluation of the subject's lipid profile (Medical Research Laboratories International, Highland Heights, KY) at week four of the Step II AHA diet determined subject eligibility for the study. At six weeks, qualified subjects were randomized (2:1) to receive 25 or 100 mg of β AET or placebo equivalent adminis-

tered buccally for 28 days. Comparison of the mean percent change from baseline of lipid markers between treatment groups defined the activity of the compound.

Statistical methods

The significance of cholesterol changes was determined by the Mann-Whitney test using GraphPad Prism software (GraphPad, San Diego, CA). Changes in HBsAg serum titers were evaluated using pair-wise comparisons between β AET and control. Results were tested for statistical significance with the exact Wilcoxon-Mann-Whitney test (two-sided). Statistical analysis was performed on the SAS® v9.1 system, with exact tests implemented using the StatXact® software package. Statistical significance was ascribed to p-values \leq 0.05 [24].

Results

Safety

Neither subcutaneous nor transmucosal administration of β AET resulted in measurable systemic toxicity as evidenced by clinical evaluations and laboratory parameters including ECGs and vital signs. Injection site reactions (edema, pain, and erythema) were reported for all subjects that received subcutaneous β AET, and were more severe than with corresponding placebo treatments.

The majority (97%) of these adverse events were mild to moderate and distributed across all dose groups including placebo treated subjects. The most common adverse events were minor laboratory abnormalities and injection site reactions. Less than 1% of the adverse events resulted in discontinuation of study treatment. There were no adverse events that resulted in reduction of dose, interruption of treatment (with continuation), blood transfusion, hospitalization, or intravenous fluid infusion. Summaries of the adverse events for the Phase I and Phase II studies combined are listed in **Tables 1 and 2**.

Pharmacokinetics following buccal administration

There was evidence of β AET absorption by transmucosal administration in all but one subject, although plasma concentrations were below the limit of detection in the majority of blood

Table 1. Summary of adverse events reported with an incidence of $\geq 5\%$ for any dose cohort: hematology, chemistry, and body temperature

	Placebo ¹ (n=60)	25 mg (n=34)	50 mg (n=10)	100 mg ¹ (n=66)	Total (n=170)
Subjects with events	55 (92%)	29 (85%)	10 (100%)	60 (91%)	154 (91%)
Investigations	43 (72%)	18 (53%)	5 (50%)	42 (64%)	108 (64%)
Lymphocyte count decreased	26 (43%)	5 (15%)	4 (40%)	26 (39%)	61 (36%)
Red blood cells urine positive	13 (22%)	1 (3%)	0 (0%)	9 (14%)	23 (14%)
Alanine aminotransferase increased	9 (15%)	2 (6%)	0 (0%)	7 (11%)	18 (11%)
Aspartate aminotransferase increased	7 (12%)	2 (6%)	1 (10%)	7 (11%)	17 (10%)
Blood sodium increased	7 (12%)	1 (3%)	0 (0%)	6 (9%)	14 (8%)
Blood bilirubin increased	5 (8%)	1 (3%)	0 (0%)	6 (9%)	12 (7%)
Haemoglobin decreased	9 (15%)	1 (3%)	0 (0%)	2 (3%)	12 (7%)
Blood alk phos NOS increased	4 (7%)	2 (6%)	0 (0%)	5 (8%)	11 (6%)
Blood triglycerides increased	6 (10%)	0 (0%)	0 (0%)	4 (6%)	10 (6%)
Blood urea increased	6 (10%)	2 (6%)	0 (0%)	2 (3%)	10 (6%)
White blood cell count decreased	5 (8%)	1 (3%)	0 (0%)	4 (6%)	10 (6%)
Gamma-glutamyltransferase increased	3 (5%)	3 (9%)	0 (0%)	3 (5%)	9 (5%)
Blood creatine phosphokinase increased	1 (2%)	2 (6%)	1 (10%)	2 (3%)	6 (4%)
Platelet count decreased	4 (7%)	0 (0%)	0 (0%)	2 (3%)	6 (4%)
Blood glucose increased	2 (3%)	1 (3%)	0 (0%)	2 (3%)	5 (3%)
Blood potassium increased	0 (0%)	2 (6%)	0 (0%)	3 (5%)	5 (3%)
Body temperature increased	1 (2%)	3 (9%)	0 (0%)	1 (2%)	5 (3%)
Neutrophil count decreased	2 (3%)	1 (3%)	0 (0%)	2 (3%)	5 (3%)

¹subcutaneous and transmucosal combined, includes injection site reactions

samples collected from both adult and elderly subjects receiving the 25 mg dose. The C_{max} values were essentially invariant by age and dose. The mean observed C_{max} from 25 mg was 6.5 ng/mL, just slightly greater than the lower limit of quantification, and 13.3 ng/mL from the 100 mg dose. Subjects that were BQL for the entire day were not included in the daily C_{max} calculation. The T_{max} was 2-4 h; β AET was not detected in any sample collected after day 4. The integrated exposure (AUC) and rate of elimination were not calculated due to the paucity of data. All placebo subjects had undetectable endogenous β AET.

Pharmacokinetics following subcutaneous administration

The plasma drug concentration profile from subcutaneous β AET microsuspension injection did not fluctuate substantially after reaching detectable levels. In the 50 mg cohort, β AET was not detected in either age group on day 1. After repeat administrations the plasma concentra-

tion ranged from 5 to 14 ng/mL in both age groups, but was frequently BQL. In the 100 mg cohorts, drug was first detected 0.5-2 hours after administration in most adults, and in all subjects thereafter. Plasma drug concentrations were similar in both age groups on days 2 and 3. The mean plasma β AET concentration was 10 ng/mL (range 5-20 ng/mL in adults and 5-28 ng/mL in the elderly). Three days after the last dose, β AET was detected in 3 of 5 adult and 2 of 5 elderly subjects (5-10 ng/mL).

β AET effects on serum cholesterol in healthy adult and elderly subjects

We found a rapid decrease in serum cholesterol levels in healthy adults not previously reported with DHEA in mice [25] or in humans [26]. Serum cholesterol was significantly decreased on day 7 in adults that received 100 mg subcutaneous β AET ($p = 0.0095$) and a significant trend was found with 100 mg transmucosal administration ($p = 0.067$) (**Figure 1**). There were no significant changes in the HDL or LDL fractions

Table 2. Summary of adverse events reported with an incidence of $\geq 5\%$ for any dose cohort: general disorder and administration site conditions

	Placebo ¹ (n=60)	25 mg (n=34)	50 mg (n=10)	100 mg ¹ (n=66)	Total (n=170)
General disorder and administration site conditions	24 (40%)	2 (6%)	10 (100%)	32 (48%)	68 (40%)
Injection site erythema	11 (18%)	0 (0%)	8 (80%)	24 (36%)	43 (25%)
Injection site pain	5 (8%)	0 (0%)	9 (90%)	27 (41%)	41 (24%)
Injection site oedema	0 (0%)	0 (0%)	8 (80%)	9 (14%)	17 (10%)
Injection site warmth	0 (0%)	0 (0%)	3 (30%)	11 (17%)	14 (8%)
Injection site mass	1 (2%)	0 (0%)	0 (0%)	9 (14%)	10 (6%)
Injection site discolouration	6 (10%)	0 (0%)	0 (0%)	3 (5%)	9 (5%)
Fatigue	3 (5%)	0 (0%)	0 (0%)	5 (8%)	8 (5%)
Pyrexia	1 (2%)	0 (0%)	0 (0%)	4 (6%)	5 (3%)
Infections and infestations	17 (28%)	6 (18%)	1 (10%)	14 (21%)	38 (22%)
Upper respiratory tract infection NOS	8 (13%)	0 (0%)	0 (0%)	8 (12%)	16 (9%)
Urinary tract infection NOS	2 (3%)	1 (3%)	1 (10%)	3 (5%)	7 (4%)
Sinusitis NOS	1 (2%)	4 (12%)	0 (0%)	0 (0%)	5 (3%)
Nervous system disorders	14 (23%)	6 (18%)	2 (20%)	14 (21%)	36 (21%)
Headache	8 (13%)	5 (15%)	1 (10%)	8 (12%)	22 (13%)
Dizziness	3 (5%)	1 (3%)	1 (10%)	3 (5%)	8 (5%)
Musculoskeletal and connective tissue disorders	15 (25%)	5 (15%)	2 (20%)	13 (20%)	35 (21%)
Back pain	7 (12%)	0 (0%)	0 (0%)	1 (2%)	8 (5%)
Arthralgia	1 (2%)	1 (3%)	1 (10%)	2 (3%)	5 (3%)
Respiratory, thoracic and mediastinal disorders	9 (15%)	7 (21%)	1 (10%)	11 (17%)	28 (16%)
Nasopharyngitis	3 (5%)	3 (9%)	0 (0%)	4 (6%)	10 (6%)
Gastrointestinal disorders	8 (13%)	3 (9%)	3 (30%)	9 (14%)	23 (14%)
Diarrhoea NOS	2 (3%)	1 (3%)	0 (0%)	3 (5%)	6 (4%)
Skin and subcutaneous tissue disorders	8 (13%)	4 (12%)	0 (0%)	10 (15%)	22 (13%)
Rash NOS	3 (5%)	1 (3%)	0 (0%)	2 (3%)	6 (4%)
Renal and urinary disorders	3 (5%)	2 (6%)	0 (0%)	3 (5%)	8 (5%)
Haematuria	1 (2%)	2 (6%)	0 (0%)	2 (3%)	5 (3%)

¹subcutaneous and transmucosal combined, includes injection site reactions

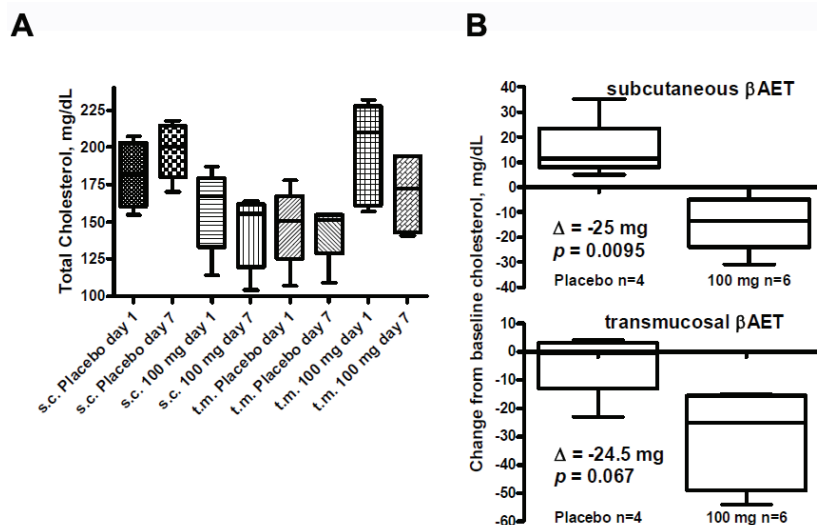


Figure 1. β AET treatment effects on cholesterol in healthy adult subjects. Normal adult subjects (age 18-55) received 4 daily doses of 100 mg β AET by subcutaneous injection (s.c.) or transmucosally (t.m., buccal). Bars represent medians with inter-quartile ranges, with the group data range bounded by upper and lower whiskers. A: total serum cholesterol (mg/dL) prior to treatment and day 7. B: Change from baseline cholesterol in placebo and 100 mg β AET treated subjects on day 7 and Mann-Whitney test results. Upper graph, s.c., lower graph, t.m.

relative to placebo or in lipid parameters at any dose in the elderly.
Phase II clinical trials

In Phase II trials elderly subjects conditioned with subcutaneous β AET did not significantly

increase their titers after either the primary or secondary HBsAg vaccination (HE2200-120), and in hyperlipidemic subjects treatment with either 25 or 100 mg transmucosal β AET for 28 days did not effect lipid parameters (HE2200-130).

Discussion

In healthy adults, but not in the elderly, β AET lowered cholesterol, which was an unexpected finding, since it was not previously observed with DHEA treatment in either rodents or humans. However, in hyperlipidemic subjects the effect completely disappeared. β AET also failed to increase HBsAg titers among the elderly. This result is in sharp contrast to the rapid immune stimulating effects of DHEA [27] and β AET observed in aged mice [10]. In both Phase II clinical failures, it appears that β AET inactivation is implicated, which is associated with chronic expression of pro-inflammatory cytokines.

Pharmacokinetic measurements suggested that the failures might have been due to rapid drug metabolism, as observed in non-human primate studies, and appeared to be consistent with up-regulated oxidative forms of 17 β -hydroxysteroid dehydrogenase (17 β -HSD) in individuals with low-grade systemic inflammation, similar to the reported effects of reductive forms of 17 β -HSD [28, 29]. Overall, our results suggest that properly formulated, β -AET may be useful as a dietary supplement to maintain health in un-inflamed normal individuals, but synthetic pharmaceutical derivatives of β AET may be necessary to treat diseases with an inflammatory etiology.

As expected from our observations in nonclinical studies, few drug related systemic adverse events were reported for either subcutaneous or transmucosal administration of β AET. Our prior investigation of β AET metabolism indicated that it is subject to extensive primary and secondary metabolism, as are DHEA, androstenediol, testosterone, and estradiol [30]. β AET pharmacokinetics in humans is consistent with these findings: drug was cleared rapidly after transmucosal administration; apparently fast enough to prevent accumulation after multiple subcutaneous doses. The drug exposure characteristics of the subcutaneous formulation were consistent with slow β AET dissolution at the injection site [31].

We have attributed DHEA's differential activity between rodents and humans to low oral bioavailability and differential metabolism. Consequently we hypothesized that parenteral administration of the DHEA metabolite, β -AET, would address these issues. However, in the present studies, the β AET plasma levels imply that the β AET disposition may have been different in target tissues between normal subjects and those with dysregulated lipids or advancing age, conditions associated with chronic low-grade inflammation [32]. Further, these intracrine effects are not necessarily detectable by β AET measurements in general circulation. Tissue specific re-regulation of steroidogenic enzymes can occur in diseases with an inflammatory etiology [28, 33]. Our data suggest that in inflammatory conditions, anti-inflammatory androstenes may be locally inactivated by perturbation of the otherwise homeostatic intracrine network [33]. For example, up-regulation of oxidative forms of 17 β -HSD would inactivate anti-inflammatory adrenal androgen metabolites such as 5-AED and β AET, while expression and function of the steroid dehydrogenases themselves are in turn subject to regulation by inflammatory cytokine signal transduction pathways and intracellular oxidative potential [34]. The implication is that an anti-inflammatory species may be metabolically eliminated in a dysregulated constitutively pro-inflammatory environment. Dysregulated inflammatory signal transduction pathways may in this fashion resist normalization mediated by members of the DHEA metabolome. The potent anti-inflammatory activity of 17 α -ethynyl- β AET in inflammation models in addition to the apparent improvement in administered potency over β AET, and identification of 17-keto- β AET as a major metabolite support the hypothesis that oxidative 17 β -HSD is an important influence [35, 36]. Thus in our Phase II trials, oxidative steroidogenic enzymes may have reduced exogenous β AET concentrations below therapeutic levels. It follows that with advancing age, chronic inflammatory conditions will not necessarily respond to DHEA treatment. This may explain the failure of DHEA and β AET to confer benefit in the context of chronic inflammatory conditions associated with hyperlipidemia and advanced age.

One possible approach to this metabolic dilemma is to identify either a naturally occurring or chemically modified anti-inflammatory compound in the androstene series that does not

require metabolic activation and is resistant to metabolism. Several compounds, such as 17 α -ethynyl-androst-5-ene-3 β ,7 β ,17 β -triol (HE3286) [35] and androst-5-ene-3 α ,7 β ,16 α ,17 β -tetrol [8] appear to meet these criteria. The anti-inflammatory activity of the ethynyl analog has been shown to be mediated, at least in part, by decreasing the activity of the inflammatory cytokine TNF α [35-39] via modulation of TNF α /MAPK/NF κ B signal transduction pathways. With this molecule anti-inflammatory effects in macrophages are observed in both rodents [35, 36] and humans (manuscript submitted). Lu et al. recently published that the 17 α -alkynylated analog of β AET reduced cholesterol in rats through up-regulation of the sterol regulatory element-binding protein-2 (SREBP-2) with subsequent increased expression of liver LDL receptors [36]. SREBP-2 mediated increases of LDL receptors is also known to occur in human liver cells [40], so it follows that β AET possesses the pharmacological activity to lower cholesterol in humans. If this is the case, signaling through the SREBP-2 pathway appears to be an additional androstenetriol activity shared by rodents and humans. Interestingly, SREBP-2 activity is regulated by the mitogen-activated kinase signaling pathway [40, 41] previously implicated in the anti-inflammatory activity of β AET and 17 α -ethynyl-androst-5-ene-3 β ,7 β ,17 β -triol [35-39].

In summary, short-term administration of β AET was safe in humans, but the drug appeared to be rapidly metabolized and pharmacokinetics were poor, even with parenteral administration. Cholesterol lowering was observed in normal but not hyperlipidemic subjects, and β AET treatment failed to enhance the response to HBsAg vaccine in elderly subjects. These divergent activities that are reported between rodents and primates may in part be attributed to chronic inflammation, which in addition to differential metabolism, provides a basis for the long standing disparity between these species and the emergence of the "DHEA conundrum" [42]

These observations suggest that natural anti-inflammatory C-19 steroids may be useful to maintain health in healthy individuals, but tissue specific inactivation of natural androstenes in the context of chronic inflammation can result in treatment failure. In these situations metabolically resistant derivatives may be necessary to successfully treat disease.

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