Effects of Prohormone Supplementation in Humans: A Review

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Abstract/Résumé

Despite a relative dearth of information on their effects, supplementation with prohormones has become a popular practice. Unlike synthetic anabolic-androgenic steroids, many of these over-the-counter androgens are produced endogenously by adrenal, gonadal and peripheral steroidogenic pathways as part of the normal sexual and reproductive hormonal milieu. It has been contended that peripheral enzymatic conversion of these prohormones to testosterone or nortestosterone (via ingestion of androstenedione/androstenediol or 19-nor-androstenedione/androstenediol, respectively) might lead to anabolic and/or ergogenic effects. Existing data suggest that acute oral ingestion of ≥ 200 mg androstenedione or androstenediol modestly and transiently increases serum testosterone concentrations in men; however, this is accompanied by greater increases in circulating estrogen(s). At doses < 300 mg/d, oral supplementation for as long as 12-weeks with androstenedione or androstenediol has no effect on body composition or physical performance and decreases high-density lipoprotein cholesterol. Similarly, oral supplementation with norandrostenedione and norandrostenediol for up to eight weeks has no effect on body

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composition or physical performance. In light of these data, new products have been developed that use alternative modes of prohormone administration (sublingual/transbuccal and cyclodextrin-complexation). Future studies should critically examine the effects of these approaches. However, within the framework of the research reviewed, over-the-counter oral prohormone supplementation is ineffective at increasing muscle mass or athletic performance. As a result of the potential health concerns that have been raised, the risk to benefit ratio of using these substances orally seems unfavorable.

La supplémentation en prohormones s'avère une pratique répandue malgré le manque d'information au sujet des effets possibles. Plusieurs de ces prohormones administrées sous surveillance pharmaceutique proviennent des glandes surrénales, des gonades et d'autres systèmes stéroïdogènes; à la différence des stéroïdes anabolisants et androgènes, ces prohormones relèvent normalement du système endocrinien associé au sexe et à la reproduction. Il est admis que la conversion enzymatique de ces prohormones en testostérone ou en nortestostérone (par la consommation d'androstènedione/androstènediol ou de 19-nor-androstènedione/androstènediol, respectivement) amène des effets anabolisants et/ou ergogènes. D'après certaines études, la consommation per os *de ≥ 200 mg d'androstènedione ou d'androstènediol augmente légèrement et temporairement la concentration sérique de testostérone chez l'homme; en même temps, il y a augmentation de la concentration des œstrogènes en circulation. Une supplémentation* per os *d'androstènedione ou d'androstènediol inférieure à 300 mg par jour durant 12 semaines n'entraîne aucun effet sur la composition corporelle et sur la performance physique, cependant le niveau de HDL-cholestérol diminue. De même, la supplémentation* per os *en norandrostènedione ou en norandrostènediol sur une durée allant jusqu'à huit semaines n'entraîne aucun effet sur la composition corporelle et sur la performance physique. Compte tenu de ces observations, de nouvelles façons d'administrer ces prohormones ont été élaborées : par voie sublinguale/transbuccale ou par complexation au moyen de la cyclodextrine. Ces différentes modalités devraient faire l'objet d'études scientifiques. Néanmoins, d'après l'analyse de la revue de littérature, la supplémentation en prohormones sous surveillance pharmaceutique ne fait pas augmenter la masse musculaire ni améliorer la performance. À la lumière des problèmes potentiels évoqués, le risque n'en vaut pas la chandelle.*

Introduction

In December of 1996, androstenedione became available for over-the-counter (OTC) sales in the United States. Subsequently, several other prohormones (e.g., androstenediol, norandrostenedione, norandrostenediol) became available OTC as well. Marketing claims have suggested that peripheral enzymatic conversion of these prohormones to testosterone or nortestosterone (via ingestion of androstenedione/androstenediol or 19-nor-androstenedione/19-nor-androstenediol, respectively) might lead to anabolic and/or ergogenic effects. Beyond the narrow scope of performance enhancement, it has also been alleged that supplementation with prohormones might be useful in partially correcting the gradual decline in testosterone, DHEA, and libido that typically accompanies the aging process (Belanger et al., 1994; Gray et al., 1991). This brief review will focus on the effect of prohormones regarding serum hormone concentrations, physical performance, and body composition. Research will be discussed in chronological order so that readers will gain an appreciation of progress in this area.

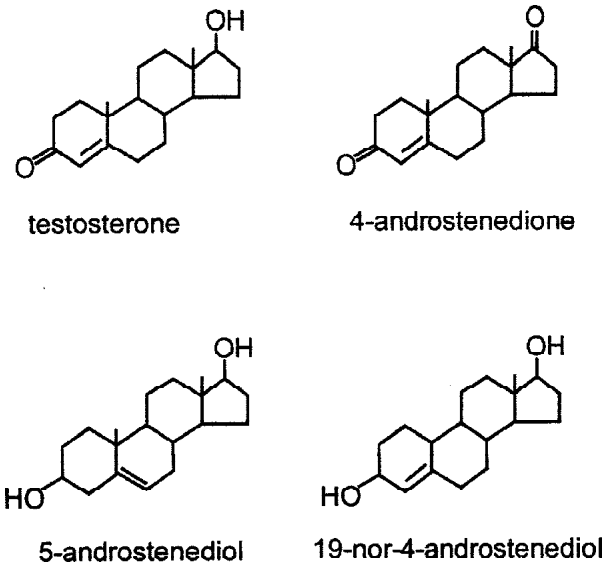

Figure 1. Chemical structures of testosterone and various prohormones.

Currently, most published research has examined the effects of oral 4-androstenedione administration in humans. Although indeed a "steroid" structurally, the potential anabolic effects of 4-androstenedione in humans have yet to be demonstrated in healthy humans. A myriad of other structurally similar prohormones are available to consumers including: 4-androstenediol, 5-androstenedione, 5-androstenediol, 19-nor-4-androstenedione, and 19-nor-4-androstenediol. While testosterone is a 19-carbon steroid with a 4,5 double bond and a keto- and hydroxyl group at positions 3 and 17 of its sterane ring, respectively, 4-androstenedione contains two keto groups and 4-androstenediol contains two hydroxyl groups at these positions. In contrast, 5-androstenedione and androstenediol have a 5,6 double bond while the 19-norsteroids contain one less carbon atom in their sterane ring structure (Figure 1). The biosynthesis of testosterone from the -dione and -diol prohormones is controlled by the ubiquitous enzymes 17 and 3 beta-hydroxysteroid dehydrogenase, respectively. Because these enzymes exist as a family of multiple isozymes, each with a specific oxidative/reductive activity, substrate specificity and cell-specific expression (Luu-The 2001; Simard et al., 1995), it is possible that prohormone ingestion might, either directly or indirectly, affect the formation of a number of sex steroids other than testosterone (e.g., dehydroepiandrosterone, estradiol, luteinizing hormone, etc.).

Review of Studies

In one of the first investigations examining the effects of oral 4-androstenedione (androstenedione) supplementation in humans, two women were given 100 mg of

oral androstenedione or dehydroepiandrosterone (Mahesh and Greenblatt, 1962). Using sampling intervals of 30 minutes for up to 90 minutes post-administration, it was shown that the oral dose of androstenedione lead to a 7-fold increase in plasma testosterone in one subject and a 4-fold increase in the other, with peak concentrations occurring at 60 minutes. Dehydroepiandrosterone supplementation led to a 4-fold increase in plasma testosterone in both women with the peak concentration occurring at 60 minutes for one woman and 90 minutes for the other. Interestingly, plasma levels of androstenedione were undetectable before supplementation in both groups and only very small increases in plasma androstenedione were found at 60 and 90 minutes in the androstenedione supplemented women. While it is unclear why only small increases in androstenedione were found, these early data suggest that oral supplementation with androstenedione or dehydroepiandrosterone may increase circulating testosterone concentrations in women. Unfortunately, the measurement of other sex steroids such as estrone and estradiol was not made.

Five years later, Blaquier and colleagues (1967) reported that 4-androstenediol (androstenediol) exhibited a 2.8-fold greater conversion to testosterone *in vivo* than 4-androstenedione. This would suggest that 4-androstenediol might have a greater anabolic effect than 4-androstenedione. Blaquier, et al. (1967) also reported that within the delta-4 pathway, androstenedione can interconvert to androstenediol before it ultimately becomes testosterone. Thus, early evidence suggests that direct administration of androstenediol may result in higher circulating testosterone concentrations than androstenedione *in vivo.* Curiously, despite these data, most *in vivo* investigations have focused upon androstenedione instead of androstenediol. Most likely, this is a result of androstenedione appearing on the market first.

Only recently has the effect of acute or chronic prohormone supplementation been examined in detail. King et al. (1999) studied 30 untrained normotestoterogenic men (19–29 yr) who were reportedly free of extraneous dietary supplements. Twenty subjects performed 8-weeks of whole-body resistance training. During weeks 1–2, 4–5, and 7–8 randomly assigned subjects consumed either androstenedione (300 mg/d in three divided doses) or placebo. The effect of a single dose of 100 mg of androstenedione was also assessed in a subset of 10 men. Acute androstenedione administration had no effect on total testosterone, free testosterone, luteinizing hormone (LH), or follicle stimulating hormone (FSH) but increased serum androstenedione concentrations by 175-350%. During training, serum estradiol concentrations were higher after 2, 5, and 8 weeks compared to baseline values in the androstenedione group. Also, serum estrone was higher at weeks 2 and 5 in the androstenedione group but this difference disappeared by week 8. Although total testosterone was unaffected, concentrations of free testosterone were significantly higher in the androstenedione group at 0 and 8 weeks. Body composition, cross-sectional areas of type I and II fibers from the vastus lateralis, and muscle strength improved similarly in both groups. The training program resulted in a significant increase in lean body mass (+ 4.7 vs. + 4.6%) and reduction in fat mass (– 11.4 vs. – 4.4%), however, no difference was noted between the androstenedione and placebo groups, respectively. These improvements are noteworthy considering that both total energy (119.9 vs. 123.1 $kJ \cdot kg^{-1} \cdot d^{-1}$) and protein (0.82 vs. 0.98 $g \cdot kg^{-1} \cdot d^{-1}$) intake in the androstenedione and placebo groups, respectively, were lower than is typically recommended for subjects engaged

in resistance training for muscle hypertrophy (McArdle et al., 1999; Williams, 2002). With regards to serum chemistry, there were no changes in low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, triglycerides, liver function enzymes, or iron and red blood cell status. There were also no changes in basal LH or FSH concentrations following training, indicating no disturbance of the hypothalamic-pituitary-testicular axis. However, there was a statistically significant decrease in high-density lipoprotein cholesterol (–12%, from 42.2 to 37.1 ng/dL) after 2 weeks in the androstenedione group. These values remained depressed at weeks 5 and 8 compared to baseline.

It has been noted that subjects in the King et al. (1999) study were untrained and had relatively high percent body fat (i.e., 21.3 and 23.5% for placebo and androstenedione groups, respectively). Because untrained subjects can substantially improve their body composition and exercise performance from training alone, it is possible that this improvement might have overshadowed any possible treatment effect. If this were the case, any improvement in body composition as a result of supplementation would be quite small relative to the large changes induced by training. However, this hypothesis seems unlikely as these results have been confirmed in similar studies (described below). Also, the high body fat of these subjects might explain in part why they had unusually high estrogen concentrations (Longcope et al., 1978). For example, these subjects' values were > 200 pmol/L whereas the normal range of serum estradiol concentrations is approximately 40–120 pmol/L. Assay differences aside, it is known that there is an enhanced conversion of androstenedione to estrogens in obese males (i.e., BMI > 30) due to peripheral aromatization in adipose tissue (Kley et al., 1980; Longcope et al., 1969, 1978; Mahesh and Greenblatt, 1962). Although it is tempting to speculate that the estrogenic responses observed in this study were due to excessive body fat, because follow-up studies have confirmed estrogenic responses to oral androstenedione supplementation in leaner subjects, it is likely that the high conversion to estrogens was due to other factors (to be described below).

Wallace et al. (1999) reported on the effects of a 12-week period of supplementation with androstenedione and dehydroepiandrosterone (DHEA) on measures of body composition, strength, and plasma hormones in a group of middle-aged men (48.1 ± 3.9 yr). Subjects received either a placebo, DHEA (100 mg/d in two divided doses), or androstenedione (100 mg/d in two divided doses) during 3 months of resistance training. These investigators, confirming the data of King et al. (2000), found no significant increase in lean body mass or strength in the DHEA or androstenedione supplemented groups in comparison to the placebo. Moreover, there was no effect of DHEA or androstenedione supplementation on prostate-specific antigen, glucose, insulin, liver function, or plasma lipid concentrations. This lack of effect on plasma lipids contrasts the lipid alterations reported by King et al. (2000). Thus, in normal, healthy middle-aged men oral supplementation with low dose androstenedione or DHEA appears to have no effect on body composition or strength during training while data on certain health parameters remains equivocal.

In a case study, a well-trained male bodybuilder (age 28 yr; 92.3 kg, ~ 5–7 % body fat) self-administered 200-400 mg/day of androstenedione in a cyclic fashion (i.e., consumed the prohormone in two 4-week cycles during weeks 1–4 [200 mg/d] and 7–10 [400 mg/d]) over a 11-week period (Antonio et al. 1999). Total

testosterone and serum chemistries did not change; however, free testosterone increased 33.5% (from 15.5 [week 0] to 20.7 [week 11] ng/dL). Body fat also increased from 7.3% (week 0) to 8.7% (week 11) as assessed by DEXA although body weight did not change. Although this study did not measure serum estrogen concentrations, any increase in body fat could be partly related to conversions of plasma androstenedione to estradiol. A consideration in this and similar studies is that some androgens lead to changes in hydration of the fat free mass (via sodium and water retention) which could be subsequently misinterpreted as increased body fat (Casaburi et al., 1996). Most body composition techniques are vulnerable to such error. Thus, within the limitations of a single-subject design, these data suggest that in a well-trained bodybuilder, chronic oral supplementation with androstenedione in modest doses may increase free testosterone; however, it may also lead to small increases in body fat.

In vivo data concerning androstenedione and androstenediol reported by Earnest and colleagues (2000) reveal effects that are interesting, yet puzzling. Compared to placebo, elevated area-under-the-curve (AUC) values were reported over a 90-minute time course for total testosterone (15%, $p < .05$) and free testosterone (23%, $p < .06$) after a single 200 mg oral dose of androstenedione in eight men. Comparatively, 200 mg of orally administered androstenediol had no effect on these variables compared to placebo. These findings contrast those of Blaquier et al. (1967), which revealed androstenediol to be more testosterogenic than androstenedione. Also, despite AUC differences in the Earnest et al. (1999) data, no group-by-time interactions were noted for either prohormone when analyzing changes across individual testosterone concentrations (either free or total) at 0, 30, 60 and 90 minutes versus placebo. Nor were significant differences found in testosterone when the androstenedione condition was compared to the androstenediol condition. Interestingly, at 90 minutes post androstenediol ingestion androstenedione concentrations were still increasing, reaching a value 103% above baseline. Although a simple interpretation of these findings is not possible, especially with the relatively small sample of men studied ($N = 8$) and truncated blood sampling period, they seem to indicate that orally administered androstenedione or perhaps androstenediol may modestly increase serum testosterone concentrations.

Using a random groups design, Leder et al. (2000) reported that in healthy men, 7 days of oral androstenedione supplementation (100 mg/day or 300 mg/day as a single dose) lead to large acute increases in 8-hour AUC for serum androstenedione (72% and 697%), estrone (74% and 196%), and estradiol (42% and 128%). Only the 300 mg dose resulted in small (34%) increase in the AUC for total testosterone. However, regardless of the androstenedione dose, basal concentrations (i.e., drawn 24 hours post-administration on days 1 and 7) of testosterone, estrone, FSH and LH were unaltered. Although the acute increases in AUC for serum estrogens were much larger than those in total testosterone, it is interesting to note that in the 300mg/day group, ~ 29% of subjects had serum testosterone concentrations that exceeded the upper limit of the normal range. In contrast, ~ 80% of subjects in the 100 mg/day group and ~ 71% of subjects in the 300 mg/day group had serum estradiol concentrations that exceeded the upper limit of the normal range. Additionally, on day 1 of the study men in the 300mg/day group experienced peak increases in total testosterone of 88% (from 493 ng/dL to 929 ng/dL) while on day 7 this increase was only 66% (from 526 ng/dL to 872 ng/dL). Whether

this effect was due to an induction of androgen-metabolizing liver enzymes, as occurs with orally administered testosterone (Nieschlag et al., 1977), is unknown. This study also demonstrates a dose response effect from oral androstenedione supplementation. In this instance, 100 mg of androstenedione only elevated serum estrogens while a 300 mg dose elevated serum testosterone as well, without increasing the proportion of subjects who exceeded normal estrogenic limits. However, as stated previously the increase in serum estrogen was always several orders of magnitude greater than those for testosterone, suggesting that these changes are of no benefit during resistance training. It should also be noted that the mean increase in testosterone seen in the 300 mg group was driven largely by two hyper-responsive subjects.

In an investigation conducted by Ballantyne et al. (2000) the acute effects of oral androstenedione supplementation were examined. In this study, basal concentrations of sex steroids were first established in 10 male subjects during a 24-hour sampling period. Subsequently, 200 mg of oral androstenedione (in two divided doses) was given for 48 hours and venous samples were drawn every 3 hours over the course of 12 hours. A final blood sample was taken on the third day, 24 hours after ingestion of the final capsule. Interestingly, results indicated that oral androstenedione supplementation lead to increases in serum androstenedione (~ 200% peak increase) and luteinizing hormone (~ 100% peak increase) without concomitant increases in serum testosterone, free testosterone, or estradiol. The fact that there were no increases in estradiol concentrations contrasts previous findings and is difficult to explain, however, there were non-significant trends for increased testosterone concentrations in the morning (~ 14%) and for increased estradiol (~ 20%) at all time points with supplementation. Since it is thought that most androstenedione tends to be converted first to estrone in the periphery (blood, bone, skeletal muscle, and adipose tissue) rather than estradiol, the measurement of serum estrone might have offered further insight into the impact of oral androstenedione supplementation on serum estrogens (Longcope et al. 1969, 1978). However, in light of previous findings, increases in estrone and estradiol concentrations might have been expected, making the failure to show an increase in estradiol puzzling. The increase in serum LH concentrations in the supplemented condition was unexpected by the authors since there was no measurable change in testosterone concentrations. One would expect that a decrease in serum testosterone, rather than an increase, would lead to the observed elevation in LH. However these hormonal patterns were not observed.

In the same study, Ballantyne et al. (2000) also examined the putative interaction between oral androstenedione supplementation and an acute bout of resistance exercise. Oral androstenedione supplementation was given as above and a whole-body resistance training bout was conducted one hour after the final 100 mg dose. Blood was sampled immediately before and after exercise and also 90-minutes later. Exercise in both the supplemented and unsupplemented (placebo) conditions lead to respective increases in total testosterone (~ 21% and ~ 26%) and free testosterone (~ 50% and ~ 20%) concentrations immediately after exercise. This change was transient, however and hormone concentrations returned to baseline by 90-minutes post-exercise. There were no significant differences between the two supplement conditions. In addition, hematocrit followed a similar profile with no differences between the groups. Thus, the brief and non-significant increases in

serum testosterone after the exercise bout were likely due to fluid shifts and hemoconcentration rather than an increased production of testosterone. LH did not change in either condition, providing further evidence that neither testosterone synthesis nor release was increased. Interestingly, there was an interaction between androstenedione supplementation and the exercise session, leading to increased serum estradiol for at least 90 minutes after the bout was terminated. Specifically, estradiol increased significantly in the androstenedione condition following exercise and remained elevated for 90 minutes (~ 40% increase from baseline and ~ 80% increase when compared to the placebo condition). Comparatively, the placebo condition resulted in no changes in estradiol concentrations. This investigation demonstrates that oral androstenedione supplementation (100 mg taken twice per day) does not increase total or free testosterone concentrations at rest or in combination with resistance exercise. However, in contrast to other investigations discussed in this review, serum estradiol was not significantly affected by androstenedione supplementation at rest but did result in an estrogenic response to exercise.

In another investigation, a prohormone supplement purported to enhance testosterone concentrations while minimizing the formation of dihydrotestosterone and estrogen (Andro-6‘: 300 mg androstenedione, 150 mg DHEA, 750 mg *Tribulus terrestris*, 625 mg chrysin, 300 mg indole-3-carbinol, and 540 mg saw palmetto) was consumed by healthy young men over an eight-week period (Brown et al. 2000). Each day during weeks 1–2, 4–5, and 7–8, subjects consumed Andro-6‘ or placebo while undergoing resistance training three times per week. Muscle strength improved similarly in the placebo and Andro-6‘ groups with no significant differences between groups. Serum free and total testosterone did not change in either group; however, serum androstenedione was higher in the Andro-6‘ group after 2, 5, and 8 weeks. Serum estradiol (weeks 2, 5, 8) and serum estrone (weeks 5, 8) were significantly elevated in the Andro-6‘ group. Thus, resistance training combined with an eight-week supplementation period with this particular combination of ingredients does not reduce the estrogenic effect of androstenedione nor increase testosterone concentrations or muscular strength.

Work from the same laboratory (Brown et al. 2000a) investigated the effects of androstenedione ingestion in healthy middle-aged men (30-56 yr). In a double-blind, randomized manner, subjects ingested 100 mg of androstenedione three times daily or a placebo for 28 days. Serum androstenedione, dihydrotestosterone (DHT), free and total testosterone, estradiol, prostate-specific antigen (PSA), and lipids were ascertained at week 0 and each succeeding week throughout the treatment period. During weeks 1–4, it was found that androstenedione supplementation resulted in significant increases in serum androstenedione (+ 300%), free testosterone (+ 45%), DHT (+ 83%), and estradiol (+ 68%). Serum concentrations of high-density lipoprotein cholesterol (HDL-C) decreased 10% during the first week of supplementation and remained depressed, confirming the findings of King et al. (2000). However, serum concentrations of total testosterone and PSA did not change. These data confirm earlier work, which shows an increase in serum estrogen and a decrease in HDL-C in response to oral androstenedione administration.

In an extremely thorough investigation dubbed “The Andro Project”, Broeder et al. (2000) compared the effects of oral androstenedione and androstenediol supplementation during 12-weeks of intense resistance training. Fifty healthy men (age 35–65 yr) were randomly assigned to a placebo, androstenedione (200 mg/d taken

in two divided doses), or androstenediol (200 mg/d taken in two divided doses) group. Each subject participated in a three day per week resistance training program that included an average of three sets of nine exercises (i.e., a total of 81 sets per week) using 60–95% of their pre-training 1 repetition maximum.

Despite an initial increase in total and free testosterone in the androstenedione group during months one and two, basal concentrations of these hormones returned to normal by the 3-month mark. Compared to week-0, concentrations of estrone, estradiol and DHEA-sulfate increased significantly in the androstenedione and androstenediol groups at week-12. Neither androstenedione nor androstenediol supplementation improved the adaptations to resistance training compared to placebo with regards to muscular strength. Unfortunately, the training program in this study may have been too strenuous or the nutritional intake inadequate, considering that it failed to positively alter body composition, even in the placebo group (i.e., no changes were noted in DEXA calculated fat-free mass or muscle mass). On a related note, relative to determining the potential anabolic effects of these supplements, subjects were probably hypoenergetic as the average energy intake was only ~ 120 kJ · kg^{-1} · d^{-1} (29 kcal · kg^{-1} · d^{-1}). In contrast, current sports nutrition recommendations for individuals undergoing intense training are ~ 3.1 kJ · kg^{-1} · d^{-1} (13 kcal · kg^{-1} · d^{-1}) higher (McArdle et al., 1999; Williams, 2002). In agreement with King et al. (1999) and Brown et al. (2000a), oral supplementation with androstenedione and androstenediol appeared to adversely affect blood lipids (i.e., decreased HDL-C and unfavorably changed the [(LDL-C/HDL-C)/(apolipoprotein A/apolipoprotein B ratio)]) when analysis of covariance was applied. This study demonstrates that ingestion of 200 mg/day of oral androstenedione or androstenediol is no better than a placebo with regards to muscular strength or lean body mass changes in middle-aged to older men and has unfavorable effects on blood lipids.

One of the most convincing studies demonstrating a lack of anabolic effects from low dose, oral androstenedione supplementation was conducted by Rasmussen et al. (2000). Using a three compartment model involving biopsies of the vastus lateralis, femoral arterio-venous sampling, and infusion of L-[*ring*-$^{2}H_{5}$]phenylalanine, values for muscle protein synthesis and breakdown were calculated. In addition, muscle protein fractional synthetic rates (FSR) were also calculated using the precursor-product model. Six recreationally active young men were examined before and after five days of oral androstenedione supplementation (100 mg/d as a single dose). Following an overnight fast, 100 mg of androstenedione had no affect on LH or testosterone, however, estradiol concentrations increased by ~ 70% during the final hour of a five hour sampling period. Also, compared to a control group of 3 men and 3 women, androstenedione did not affect muscle protein synthesis, FSR, or muscle protein breakdown. In fact, net protein balance (synthesis minus breakdown) tended to be more negative in the androstenedione group ($P = 0.09$).

In contrast to the aforementioned androstenedione and androstenediol research, there is only one published study that has examined the effects of norandrostenedione and norandrostenediol (Van Gammeren et al., 2001). Subjects in this investigation were matched for body weight and percentage body fat and randomly assigned to a placebo or a norsteroid-supplemented group (156 mg of norsteroids daily – 100 mg of norandrostenedione and 56 mg of norandrostenediol

in a single dose). Each subject participated in a resistance training program four days per week over an eight-week treatment period. Body composition (via DEXA), circumference of the arm, waist, and thigh, one-repetition maximum bench press strength, dumbbell bench press power, and mood states were assessed. Unfortunately, because there were no significant changes in any of the parameters measured for either group, the training program in this study was ineffective. Although this precludes a definitive interpretation of the data relative to norsteroid supplementation, it seems extremely unlikely that the addition of 156 mg/day of these substances orally elicits ergogenic effects in recreational bodybuilders.

Table 1 compares the various strategies used to determine the physiological responses to prohormone supplementation from ten recent studies. From these data three important observations emerge. First, with the exception of Ballantyne et al. (2000) all studies that measured estrogen(s) have noted statistically significant increases from oral prohormone administration. Second, increases in serum testosterone have been equivocal and appear to be dose dependent. And third, small but statistically significant reductions in HDL-C seem to occur when doses ≥ 200 mg are consumed for ≥ 4 weeks.

Sex Differences in Steroid Metabolism

While the aforementioned studies examined the effects of androstenedione and androstenediol in men, there are several interesting studies that have compared the effects in men vs. women. Not surprisingly, these studies indicate potential sex differences in androgen metabolism. In a very detailed investigation examining the interconversions of androstenedione and testosterone, Horton and Tait (1966) provide evidence for the apparent sex differences seen with oral androstenedione supplementation. Using a double isotope derivative technique, it was demonstrated that with intravenous administration of androstenedione and testosterone in women, about 60% of plasma testosterone is derived from androstenedione while only 2.8% of the plasma androstenedione is derived from testosterone. Therefore, the conversion of androstenedione to testosterone contributes largely to the circulating testosterone concentrations in women. In contrast, in men only about 0.30% of plasma testosterone is derived from androstenedione while about 37% of plasma androstenedione is derived from plasma testosterone. Therefore, men seem to preferentially convert testosterone into androstenedione and the contribution of androstenedione to circulating testosterone concentration is minimal.

In this investigation, the conversion rates for oral and intravenous infusions were also compared. From these data, it appears that of the intravenously infused androstenedione, 5.9% enters the plasma as testosterone while only 1.8% of the orally administered androstenedione enters the plasma as testosterone. Interestingly only 6.3% of the orally administered androstenedione appears in the plasma as androstenedione while 100% of the infused androstenedione appears in the plasma. Given the low plasma appearance of orally administered androstenedione and its minute subsequent conversion to testosterone, data from this investigation suggest that the liver extensively metabolizes androstenedione to non-testosterone metabolites, including estrogen (Horton and Tait, 1966). Although the formation of testosterone may be significant in the gut, the enzymatic environment of the liver appears to rapidly inactivate any newly formed testosterone before it can

Table 1 Studies Examining Physiological Responses to Prohormone Administration in Humans.

Reference	n	Subject characteristic(s)	Prohormone	Dosage regimen	Treatment duration	Plasma T response	Plasma E reponse	HDL-C response	Body composition	Exercise performance
King et al., 1999	30	Healthy, normal young males	4-dione	100 mg TID	8 wk	NC	↑ E1 and E2	↓	NC	NC
Wallace et al., 1999	40	Middle-aged males	4-dione, DHEA	50 mg BID, 50 mg BID	12 wk	NC, NC	NR, NR	NC, NC	NC	NC
Antonio et al., 1999	1	Young Bodybuilder	4-dione	200 mg SD, 400 mg SD	8 wk	↑ Free T	NR	NC	Fat mass ↑ Lean body mass ↓	NR
Earnest et al., 2000	8	Healthy young males	4-dione, 4-diol	200 mg SD, 200 mg SD	Acute (single dose)	↑ Total T, NC	NR, NR	NR, NR	NR	NR
Leder et al., 2000	42	Healthy young to middle age males	4-dione	100 mg SD, 300 mg SD	7 days	NC, ↑ Total T	↑ E1 and E2, ↑ E1 and E2	NR, NR	NR	NR
Ballantyne et al., 2000	10	Healthy young males	4-dione	100 mg BID	2 days	NC	NC	NR	NR	NR
Brown et al., 2000	20	Healthy young males	4-dione	100 mg TID	8 wk	NC	↑ E1 and E2	NR	NC	NC
Brown et al., 2000	55	Healthy young to middle-aged males	4-dione	100 mg TID	4 wk	↑ Free T	↑ E2	↓	NR	NR
Broeder et al., 2000	50	Healthy middle age to older males	4-dione, 4-diol	100 mg BID, 100 mg BID	12 wk	NC, NC	↑ E1 and E2	↓, ↓	NC	NC
Rasmussen et al., 2000	6	Healthy young males	4-dione	100 mg SD	5 days	NC	↑ E2	NR	NR	NR
Brown et al., 2000	8	Healthy, young, resistance trained males	Cyclodextrin-complexed 4-diol	21.4 mg	Acute (single dose)	↑ Total and free T	↑ E2	NR	NR	NR

Note. TT = total testosterone, FT = free testosterone, E1 = estrone, E2 = estradiol, BID = twice per day, TID = three times per day, SD = single dose, NR = not reported, *See text for details.

enter the systemic circulation (Nieschlag et al., 1975). In fact, it appears that approximately 98% of the testosterone formed from oral androstenedione is extracted in the liver with a substantial percentage undergoing conversion to estrogens (Nieschlag et al., 1975; Wang and Swerdloff, 1996). Therefore only 2% of the small amount of testosterone produced from androstenedione in the gut reaches the blood. These data provide an explanation for the recent research in men showing no change in serum testosterone but increases in estrogens with low dose, oral androstenedione administration. This relatively poor bioavailability with oral androstenedione relative to injected androstenedione is also the case with orally administered testosterone, which has been shown to be rapidly degraded in the gastrointestinal tract by microbial flora and the liver (Conway et al., 1988; Nieschlag et al., 1975; Pitha et al., 1987). In summary, men tend to more easily convert testosterone to androstenedione whereas women seem to more easily convert androstenedione to testosterone. These data may have important implications for increasing androgen levels, restoring libido, and preventing sarcopenia in postmenopausal women (Morley, 2001).

Alternative Modes of Administration

As a result of the poor bioavailability and lack of efficacy of orally administered androgens, our research group has completed a number of pilot studies examining the effects of sublingual/transbuccal (SLT) administration. Collectively, our data indicate (a) SLT administration of androstenediol results in greater increases in serum testosterone compared to oral administration, (b) elevations in serum estrogens appear to be considerably less using SLT androstenediol, and (c) complexation of androstenediol with hydroxypropyl-beta cyclodextrin (HPB), a carbohydrate ring structure that facilitates absorption through the oral mucosa, leads to substantial increases (i.e., exceeding the upper limit of the normal range in men) in serum testosterone at 1/4 to 1/8 of the comparable oral dose. Using a placebo-controlled, crossover design we recently examined the acute hormonal responses in five young (average age: 27.5 yr), lean (average body fat: 12.5%) men with at least two years of weight training experience. Relative to point C we observed peak testosterone concentrations of approximately 1292 ng/dL using a 15 mg dose of HPB androstenediol, while 25 and 50 mg doses of HPB androstenediol led to peak increases of approximately 1585 and 1700 ng/dL (unpublished observations, Figure 2). Despite an average increase in estradiol of approximately 35% during the 15 mg condition (data not shown), this difference was not statistically significant. Unfortunately, due to a freezer malfunction, we were unable to determine estradiol responses to the 25 and 50 mg conditions. For this reason, we cannot rule out that these doses of HPB androstenediol might lead to statistically significant estrogenic responses.

These increases in testosterone agree with a recent double-blind, placebo-controlled crossover study conducted by Brown et al. (2002). Eight men experienced in strength training had peak increases of 87% (from 888 ng/dL to 1660 ng/dL) in total testosterone and 103% (from 86.2 pmol/L to 175.4 pmol/L) in free testosterone after a 20 mg dose of HPB androstenediol. Interestingly, in our studies (but not in Brown et al., 2002) the observed increases in serum testosterone

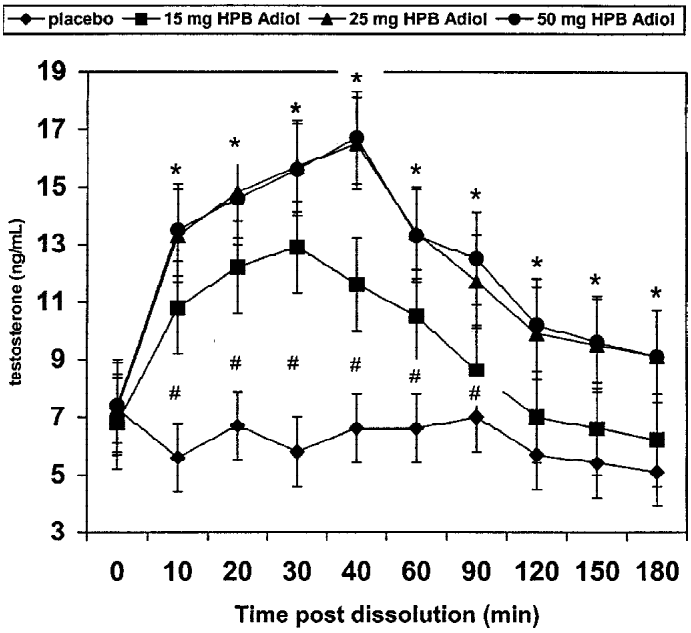

Figure 2. Total testosterone responses to a single dose of 15, 25, and 50 mg hydroxypropyl beta cyclodextrin-complexed 4-androstenediol (HPB Adiol) in men. Values represent mean testosterone concentrations in ng/mL ± SE (N = 5). *Indicates significant difference (P < .01) when compared to concentrations in the placebo condition, at baseline (minute 0) and the corresponding 15 mg condition. #Indicates significant difference (P < .01) when compared to the corresponding placebo condition and to the baseline concentration. No differences between the 25 and 50 mg conditions were noted. To convert testosterone from ng/mL to nmol/L, multiply by 3.467.

were not accompanied by statistically significant changes in estradiol, at least over a three-hour sampling period. In the Brown et al. (2002) study, estradiol concentrations increased by 30 minutes, reaching a peak value 75% above baseline (from 80 to 140 pmol/L) 180 minutes after supplementation. Interestingly, upon analysis by an independent laboratory, the supplement in the Brown et al. (2002) study was found to contain a small amount (3.7 mg) of androstenedione. What role this may have played in the observed estrogenic response is unknown. Collectively, these observations suggest that sublingual administration of prohormones is not subject to liver first pass metabolism and therefore may bypass metabolic inactivation and/or conversion to other compounds. This hypothesis is consistent with existing data comparing oral vs. sublingual testosterone administration (Nieschlag et al., 1975, 1977) as well as cyclodextrin-complexed testosterone (Pitha et al., 1987).

These findings are also interesting because as indicated by Brown et al. (2000a) and Mauras et al. (2000), large increases in circulating testosterone may be necessary to induce changes in strength and/or body composition. Therefore,

the small changes in testosterone concentrations seen with oral prohormone administration would not be expected to impact muscle mass. However, the substantial increases observed in response to HPB androstenediol raise interesting questions as to whether or not the increased androgen concentrations could impact muscle size or strength. Further, while these new findings in no way overshadow the published data on androstenedione, they nonetheless provide valuable insight into the potential differences of SLT androstenediol and HPB androstenediol on circulating testosterone. Future research is necessary to confirm/refine these responses and determine if long-term supplementation with SLT androstenediol or HPB androstenediol results in adverse health risks.

Conclusion

Although relatively few studies have examined the effects of prohormone administration in humans, the current literature reveals a number of physiological effects that reinforce their role as biologically active steroidal compounds. These effects, however, are contrary to the marketing claims of increased muscle mass, reduced fat mass and heightened physical performance. However, it is important to note that the majority of existing studies have focused upon low dose, oral androstenedione as opposed to other prohormones or alternative modes of administration. Thus, to conclude that *all* prohormones are ineffective and potentially dangerous would be premature at this time.

The consensus among studies is that oral androstenedione supplementation elevates circulating estrogens, induces small but statistically significant decreases in HDL-C, and only modestly raises testosterone concentrations at higher (≥ 200 mg) doses. Relative to the effects of prohormones on the cardiovascular system, the long-term implications of transient negative changes in blood lipids (i.e., 3–6 mg/dL reductions in HDL-C) have yet to be elucidated as the risk of sustaining a cardiac event is typically inferred from cross-sectional and longitudinal epidemiological studies. In addition, because estrogen may have atheroprotective effects (Babiker et al., 2002; Dimitrova et al., 2002), measuring additional inflammatory and atherothrombotic markers (e.g., homocysteine, C-reative protein) would add greatly to our collective understanding of how various prohormones affect cardiovascular health. However, due to the lack of efficacy of oral androstenedione supplementation in men, its theoretical risks seem to far outweigh any potential benefits on strength and body composition.

While some health risks have been noted, thus far none of the prohormones tested appear to be overtly toxic as no elevations in clinically relevant tissue enzymes (alanine aminotransferase, aspartate aminotransferase, creatine kinase, gamma-glutamyltransferase, lactate dehydrogenase) have been observed (Brown et al., 2000; King et al., 1999; Wallace et al., 1999). This contrasts the well-established hepatotoxicity of many oral 17-alpha-alkylated anabolic steroids (Dickerman et al., 1999; Pertusi et al., 2001). Disturbances in the hypophyseal-pituitary-gonadal axis (e.g. reductions in luteinizing hormone) also appear to be minimal during androstenedione administration, again contrasting the effects of elicit anabolic-androgenic steroids. Whether more prolonged (> 8–12 weeks) androstenedione supplementation is safe or useful remains uncertain, but appears unlikely. In this regard, although label directions for many prohormones suggest a cycling strategy

(e.g., 2–4 weeks "on" followed by a similar amount of time "off"), it is unclear whether consumers are heeding this advice, or instead using prohormones chronically. If the latter is true, consumers could be exposing themselves to unnecessary health risks.

The physiological effects of androstenediol and norsteroid supplementation are largely unknown at this time. However, for the same reasons outlined earlier, oral administration of these compounds seems unlikely to yield favorable results. If alternative modes of administration can consistently elevate testosterone (or nor-testosterone) in the absence of deleterious effects blood lipids or the prostate, such changes might be beneficial in exercising and/or aged populations. One could speculate that consistent exposure to short-term elevations in plasma androgens (especially testosterone) over several months or years via supplementation with prohormones might lead to increased skeletal muscle protein accretion. Conversely, if testosterone remained unchanged but plasma estrogen(s) were elevated, increased fat-mass might occur. Obviously, the observed differences in testosterone and estrogen responses to supplementation make it difficult to ascertain exactly how various prohormone supplements might affect body composition in men. Also, because of their lower baseline levels of androgens and preferential conversion of androstenedione to testosterone, we speculate that women may have a greater increase in testosterone (or nortesterone) from prohormone supplementation. However, the ethical issues surrounding androgen supplementation in post-menopausal or athletic females without physician supervision need to be considered.

In most athletic organizations, use of prohormones is banned. However, many athletes could unknowingly test positive because many prohormone package labels do not provide warnings that they may contain banned substances. In fact, Catlin et al. (2000) recently reported that seven of eight commercially available supplements claiming to contain only androstenedione were grossly mislabeled and in fact, contaminated with 19-norandrostenedione, leading to positive test results for urinary 19-norandrosterone. This study also indicated that oral doses of 19-norandrostenedione as small as 10 mg are absorbed and excreted as 19-norandrosterone and 19-noretiocholanolone (markers of nandrolone use in athletes). Finally, Catlin et al. (2000) pointed out that ingestion of androstenedione could result in the stimulation of a latent metabolic pathway leading to the formation of 19-norsteroids. Thus, it would be wise for competitive athletes who are drug tested to refrain from using all prohormones.

Given the popularity of prohormones and the wide array of clinical effects that androgens may have on health (e.g., alterations in blood lipids, cardiovascular disease risk, bone density, immunocompetence, libido, visceral adiposity, insulin sensitivity, etc.) it is obvious that more research in this area is needed. In addition, it is our experience that many consumers of these supplements use more than one prohormone at a time. Thus, studies on single androgens (although critical for uncovering mechanisms) are somewhat limited in their generalizability to the public. Admittedly, uncovering the full effects of prohormones will be a complex task because of the numerous inter-related factors that are known to influence individual responses to androgen administration such as genetic polymorphisms of the androgen receptor and hormonal interconversions at the paracrine level. In addition, as with all studies that measure serum variables, it is important to note that full disclosure of hormone responses requires sufficiently frequent blood sam-

pling and (ideally) the use of newer biostatistical procedures that provide information about hormone burst properties (amplitude, frequency, mass) and half-life. In contrast, all prohormone studies to date have used AUC analyses either with or without log transformation, or have compared hormone responses at discrete time points with ANOVA. This lack of uniform treatment and analysis of hormone data should be considered in future prohormone research.

It is acknowledged that androgen administration may predispose some individuals to health risks, however, appropriately controlled human trials involving large sample sizes, analysis of sex differences, dose response comparisons, duration of use issues and documentation of side effects must continue so that an accurate determination of the risk-to-benefit ratio of *all* prohormones can be made. One fact is relatively clear at this point, within the framework of the empirical evidence to date, there seems to be no good reason to use oral androstenedione.

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