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Estrogen or Testosterone Increases Self-Reported Aggressive Behaviors in Hypogonadal Adolescents

JORDAN W. FINKELSTEIN, ELIZABETH J. SUSMAN, VERNON M. CHINCHILLI, SUSAN J. KUNSELMAN, M. ROSE D'ARCANGELO, JACQUELINE SCHWAB, LAURENCE M. DEMERS, LYNN S. LIBEN, GEORGIA LOOKINGBILL, AND HOWARD E. KULIN

Department of Pediatrics (J.W.F., M.R.D'A., G.L., H.E.K.), The Center for Biostatistics and Epidemiology (V.M.C., S.J.K.), Department of Pathology (L.M.D.), The Pennsylvania State University, College of Medicine, Hershey, Pennsylvania 16802; Departments of Biobehavioral Health (J.W.F., E.J.S.), Human Development and Family Studies (J.S.), and Psychology (L.S.L.) College of Health and Human Development, University Park, Pennsylvania 16802

ABSTRACT

A randomized, double-blinded, placebo-controlled cross-over clinical trial was used to determine the role of sex steroids on the development of aggressive behaviors in 35 boys and 14 girls. Depo-testosterone (to boys) or conjugated estrogens (to girls) was administered in 3-month blocks alternating with placebo at three dose levels approximating early, middle and late pubertal amounts.

The Olweus Multifaceted Aggression Inventory was administered after each placebo and treatment period to ascertain the effect of sex steroids on self-reported aggressive behaviors. We employed a strict intent-to-treat analytical model. The data demonstrated significant hormone effects on physical aggressive behaviors and aggressive impulses, but not in verbal aggressive behaviors nor aggressive inhibitions in both boys and girls. These results are the first to causally relate the administration of physiological doses of sex steroids to changes in aggressive behaviors in adolescents. (*J Clin Endocrinol Metab* **82:** 2423–2438, 1997)

AGGRESSIVE, ANTISOCIAL and violent behavior involving youth is a significant public health problem in America. Forty nine percent of boys and 28% of girls in the eighth through tenth grades report having been in at least one fight involving physical aggression or a weapon during a 1-yr period (1). Eighty percent of siblings engage in violence toward each other, with higher rates in boys, especially those without sisters (2, 3). Adolescents are offenders in 24% of all violent crimes leading to an arrest (4). In 1990, 52% of those arrested for homicide and nonnegligent manslaughter were younger than 25 yr of age; 15% were younger than 18 yr (5, 6). The rate of murder charges for youths younger than age 18 yr has increased dramatically in recent years (6).

The causes for this aggressive and violent activity among teens are not known. Both social and biological factors may contribute to these behaviors (7, 8). There is a small but growing literature on normal adolescents, showing relationships between the physical changes of puberty or endogenous sex hormone levels and behaviors of various types (9–26). With regard to aggression and hormones in adolescents, the few extant studies have concentrated on the relationship of this behavior to the physical changes of puberty or endogenous sex steroids (9–16, 20, 26). All studies were observational and most used correlational analyses, thereby limiting the possibility of establishing a causal role for hormones in the behavioral changes noted.

The goal of the present study was to investigate the role of sex steroids on self-reported aggressive behavior by utilizing hormone-deficient adolescents to whom sex steroid therapy could be ethically administered and withdrawn while sequential behavioral assessments were undertaken. Two questions were posed in the investigation: First, could administered sex steroids affect aggressive behaviors? Second, would the behavioral effects for boys be different from the behavioral effects for girls?

Subjects and Methods

Subjects

All patients referred to the Pediatric Endocrine Clinic of the Milton S. Hershey Medical Center (Hershey, PA) with complaints of pubertal delay were potential enrollees. Only two candidates refused enrollment. Others were not included if their history involved chronic illness, intellectual deficits, or ingestion of medication that might affect behavior. Of 58 enrollees, 3 subjects withdrew from the study before visit 1, because they found the extra time required for behavioral testing burdensome. Six subjects were entered into the study protocol in a nonrandomized fashion, and their data are not included in the primary analysis. Six individuals started the protocol at mid dose levels based on relatively advanced age and/or prior hormone therapy.

Data from 49 patients contributed to the current analyses. The actual numbers and gender of participants who provided data at each treatment period are shown in Table 1. The mean age at first visit of all subjects was 13.6 yr ± 1.85 (SD) yr (range 10–19 yr). Fifteen patients had primary gonadal disease (including 9 girls with gonadal dysgenesis); 8 patients had documented gonadotropin deficiency, and 26 patients (24 of whom were boys) were classified as constitutional delay in puberty.

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Address all correspondence and requests for reprints to: Jordan W. Finkelstein, The Pennsylvania State University, E-315 Health and Human Development, University Park, Pennsylvania 16802. E-mail: jwf3@psu.edu.

TABLE 1. Study sample size for each treatment regimen (M = male; F = female)

Score	Placebo		Low		Middle		High	
VAAA	M:35	F:14	M:27	F:13	M:30	F:13	M:28	F:14
PAAA	M:35	F:14	M:26	F:13	M:30	F:13	M:27	F:14
VAAP	M:35	F:14	M:27	F:12	M:31	F:13	M:28	F:14
PAAP	M:35	F:14	M:27	F:13	M:31	F:13	M:28	F:14
AI	M:35	F:14	M:27	F:13	M:29	F:13	M:29	F:14
AIR	M:35	F:14	M:27	F:12	M:30	F:13	M:28	F:14

VAAA, Verbal aggression against adults; PAAA, physical aggression against adults; VAAP, verbal aggression against peers; PAAP, physical aggression against peers; AI, aggressive impulses; AIR, aggressive inhibitory responses.

TABLE 2. Testing protocol

Visit	1	2	3	4	5	6	7	8
Group X	Baseline	Placebo	Low	Placebo	Middle	Placebo	High	Placebo
Group Y	Baseline	Low	Placebo	Middle	Placebo	High	Placebo	High[a]

[a] High dose for permanently hypogonadal subjects, repeat placebo for constitutionally delayed subjects.

Pill and prefilled syringe counts were used to ensure protocol compliance in addition to hormone measurements. We were not able to control for the effects of physical activity, which could affect either hormone levels or behavior.

This study was approved by the Milton S. Hershey Medical Center Institutional Review Board. Informed consent was obtained from the parents of all subjects.

Experimental design

The experimental design was a randomized, double-blind, placebo-controlled, cross-over trial. Subjects were randomly assigned to initially receive either hormone exposure (group Y, Table 2) or placebo (group X, Table 2). Sex steroids were administered in three dose levels approximating early, middle, and late pubertal amounts of hormone exposure. Oral, daily conjugated estrogen (Premarin, Wyeth-Ayerst Pharmaceuticals, Philadelphia, PA) was administered to girls at 0.15 mg (low dose), 0.3 mg (mid dose), and 0.6 mg (high dose). Testosterone was given to boys by im injection every 2 weeks at 25 mg (low dose), 50 mg (mid dose), and 100 mg (high dose). Each 3-month hormone exposure period was accompanied by 3 months of placebo administration. There was successful adherence to this schedule because the median treatment/placebo interval ranged from 2.9–3.0 months.

Endocrine testing

Hormone analyses of blood for androgens and estrogens and of urine for gonadotropins were performed in each patient at each clinic visit. Measurements included blood levels of total testosterone and estrone sulfate and urine levels of LH and FSH. The Core Endocrine Laboratory of the Milton S. Hershey Medical Center performed all hormone tests using standard RIAs (27–29). Hormone levels served to monitor exogenous *vs*. endogenous sex steroid levels (*i.e.* the on and off treatment periods) and to assess compliance with treatments.

Behavioral testing

A modification (20) of the Olweus Multifaceted Aggression Inventory (OMAI) (30, 31) was self-administered by subjects to assess the effects of sex steroids on self-reported aggressive behaviors. The instrument employs a 6-point Likert scale that permits an adolescent to rate how much a sentence describes his/her own aggressive actions or thoughts or feelings. The original instrument consisted of four subscales: Verbal aggression against adults (VAAA), physical aggression against peers (PAAP), aggressive impulses (AI), and aggressive inhibitory responses (AIR). Finkelstein *et al.* (20) have reported the use of the OMAI in English school children.

Because additional subscales might expand the range of aggressive behaviors that subjects might report, two subscales were added in the present investigation: Physical aggression against adults (PAAA) and verbal aggression against peers (VAAP). The items for PAAA and VAAP were constructed by modifying the wording of the corresponding PAAP and VAAA subscales. Satisfactory psychometric characteristics of the original (30, 31) and modified (unpublished data) OMAI have been demonstrated. Olweus (31) validated the OMAI by comparing subject's self-reports to reports by teachers and peers and reported coefficients of 0.45–0.60. Reliability coefficients (Kendall's tau-b) for the current instrument were performed between these subjects and a group of normal adolescents from central Pennsylvania who were in early puberty. These coefficients ranged from 0.90–0.93.

Statistical analysis

All clinical, laboratory, and behavioral data were entered into an Ingres database and verified. Sample size calculations revealed that for 80% statistical power and a 5% significance level, 16 boy and 16 girl subjects would be needed to detect a difference of 1 SD in any of the aggression response variables.

The model for the ANOVA consisted of the following effects. Treatment is the main effect in the design because it tests the results of hormone administration. Treatment contains the four categories of placebo, low, middle, and high dose. The cross-over design allows this parameter to be a within-subject test. Having each subject act as his/her own control yields a more powerful test than if comparisons were made between subjects in a parallel design. The following effects were also included in the model: sequence (receiving the drugs in the order treatment-placebo or placebo-treatment); sex (effect of gender); subject (nested within sex and sequence—a random effect), an error term for the between subject effects of sex and sequence; carryover (accounts for any residual or carryover effects of having received prior therapy, either on or off hormone); visit (accounts for changes that take place over time that cannot be accounted for by the treatment); and sex by treatment interactions within subject (allows for the effect of treatment to vary between the sexes).

All means were adjusted for the model effects. Significance levels for the pairwise comparisons were adjusted using a Bonferroni correction factor; there were three pairwise comparisons (three dose levels) for each gender.

Results

ANOVA was first performed for the entire group of subjects (Table 3). Because there were highly significant differences detected for treatment effects in three OMAI subscales and for sex effects in five subscales, pairwise comparisons were performed for each OMAI subscale by gender. All placebo scores were combined so that aggressive behavior at each treatment dose level was compared with the combined placebo scores from all previous placebo treatment periods. All means were adjusted for the factors described above in the model. Table 4 presents the adjusted mean subscale scores by sex at each dose level.

TABLE 3. ANOVA *P* values for entire study group

Model effect	VAAA	PAAA	VAAP	PAAP	AI	AIR
Between subjects						
Sex	0.003	0.02	0.02	0.01	0.01	0.31
Sequence	0.99	0.64	0.93	0.16	0.23	0.91
Subject	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Within subjects						
Treatment	0.17	0.02	0.28	0.02	0.01	0.88
Visit	0.33	0.09	0.21	0.03	<0.001	0.18
Carryover	0.72	0.08	0.95	0.04	0.01	0.50
Sex by treatment interaction	0.88	0.63	0.77	0.09	0.18	0.63

TABLE 4. Aggression scores: model estimated mean ± SE by dose level and sex

Subscale	Placebo	Low dose	Mid dose	High dose
Boys				
VAAA	16.9 ± 0.8	17.5 ± 1.7	19.2 ± 1.7	16.8 ± 1.6
PAAA	15.9 ± 0.8	16.8 ± 1.7	18.8 ± 1.7	17.4 ± 1.6
VAAP	18.0 ± 0.9	19.4 ± 2.0	18.7 ± 1.9	18.0 ± 1.9
PAAP	19.1 ± 0.9	20.0 ± 1.9	22.2 ± 1.8	21.3 ± 1.8
AI	10.0 ± 0.6	11.6 ± 1.3	12.0 ± 1.3	11.5 ± 1.2
AIR	13.0 ± 0.9	11.6 ± 2.0	12.8 ± 1.9	12.1 ± 1.9
Girls				
VAAA	11.4 ± 0.5	12.2 ± 1.4	13.2 ± 1.4	11.9 ± 1.2
PAAA	11.5 ± 0.5	13.7 ± 1.5	15.1 ± 1.4	13.0 ± 1.2
VAAP	13.5 ± 0.6	15.5 ± 1.7	15.2 ± 1.6	13.0 ± 1.4
PAAP	13.6 ± 0.6	17.3 ± 1.6	17.4 ± 1.6	15.0 ± 1.4
AI	6.88 ± 0.4	10.2 ± 1.1	9.65 ± 1.1	8.0 ± 0.9
AIR	13.6 ± 0.6	14.0 ± 1.7	13.8 ± 1.6	13.1 ± 1.4

Table 5 shows the increase in subscale scores following hormone administration, and the corrected level of significance of this increase at each dose level compared with placebo. Using the Sign test, 13 of 18 comparisons for boys ($P < 0.001$) and 16 of 18 comparisons for girls ($P < 0.0001$) showed increases in aggressive behaviors during treatment periods.

Figure 1 shows the percent change in aggression scores after hormone treatment compared with placebo baseline. At the low dose (0.15 mg) of conjugated estrogen, girls showed a 48% increase in aggressive impulses scores ($P = 0.003$) and a 28% increase in physical aggression against peers scores ($P = 0.02$). Boys showed no treatment effects at the low (25 mg) dose of testosterone.

At the mid dose (50 mg testoterone) boys showed a 19% increase in aggressive impulses scores ($P = 0.06$), a 17% increase in physical aggression against peers scores ($P = 0.02$), and an 18% increase in physical aggression against adults scores ($P = 0.03$). At the mid dose (0.3 mg conjugated estrogen) girls showed a 40% increase in aggressive impulses scores ($P = 0.01$), a 28% increase in physical aggression against peers scores ($P = 0.02$), and a 31% increase in physical aggression against adults scores ($P = 0.01$).

At the high dose (100 mg testosterone for boys and 0.6 mg conjugated estrogen for girls) there were no significant increases in aggressive behaviors scores for either boys or girls.

Median hormone values appear in Table 6. The increases in concentrations of testosterone (in the boys) and estrone sulfate (in the girls), along with decreases in gonadotropins, indicate that subjects were receiving the appropriate amounts of hormone or placebo material. The reciprocal relationship between sex steroids and gonadotropins confirms that exogenous sex steroids suppressed endogenous gonadotropins.

Discussion

The classical experimental approach for establishing a role for a hormone is that of ablation-replacement (32). That is, the effect of removing a presumed hormone source (ablation) can be reversed by administration of a test substance (replacement). These conditions can be approximated by studying girls and boys with delayed puberty to whom physiological doses of estrogen or androgen can be administered in a graded fashion and withdrawn for short periods over the course of a few years. This investigation is the first to use the hormone replete/hormone deplete model during pubertal development in adolescents.

The first question formulated in this study is whether administered sex steroids can influence self-reported aggressive behaviors. The increases in aggressive impulses and in the two physical aggression subscales demonstrate that statistically significant behavioral change was observed following the administration of depo-testosterone in boys or conjugated estrogen in girls. Thus the significant behavioral score changes obtained were caused by hormone-derived effects and were not just random variations in self-reports. The lack of significant increases in self-reported verbal aggressive behaviors is unexplained but may reflect the increased physical rather than verbal violence currently seen in society (1–6).

The second question posed in this study is whether the behavioral effects of hormone treatment would be different for boys and girls. Although the administered hormone effects did not differ significantly by gender (Table 3: no significant sex by treatment interaction), there are differences in the absolute scores between boys and girls. Boys reported higher aggression scores than girls on all subscales (with the exception of AIR) at all dose levels. This finding has been reported previously, (20) and may reflect gender differences in socialization wherein boys are expected to be more aggressive than girls.

Gender differences in self-reported aggressive behaviors (7, 8) may also reflect the influence of prenatal exposure of the fetal brain to the organizing influences of sex steroids (33, 34), but the data reported by Finkelstein *et al*. (20) suggest that aggressive behavior may be a stable characteristic of adolescents that may be independent of gender.

The measurement of aggression was assessed using the OMAI, the only instrument designed solely for evaluating self-reported aggressive behaviors specifically in adoles-

TABLE 5. Changes in aggression scores (±95% CI) and corrected significance of each treatment dose

Subscale	Low − placebo	Mid placebo	High placebo
Boys			
VAAA	0.7 (−1.6, 2.9)	2.3 (0.1, 4.5)	−0.1 (−2.1, 1.9)
PAAA	0.9 (−1.4, 3.2)	2.8 (0.7, 5.0) $P = 0.03$	1.5 (−.6, 3.6)
VAAP	1.5 (−1.2, 4.1)	0.7 (−1.7, 3.2)	−.002 (−2.3, 2.3)
PAAP	0.9 (−1.5, 3.4)	3.2 (0.9, 5.5) $P = 0.02$	2.3 (0.1, 4.4)
AI	1.6 (−0.12, 3.3)	1.9 (0.3, 3.6)	1.4 (−0.1, 3.0)
AIR	−1.4 (−4.0, 1.2)	−0.2 (−2.7, 2.3)	−0.9 (−3.2, 1.4)
Girls			
VAAA	0.8 (−1.8, 3.3)	1.7 (−0.7, 4.2)	0.5 (−1.7, 2.6)
PAAA	2.2 (−0.4, 4.7)	3.6 (1.2, 6.1) $P = 0.01$	1.4 (−0.7, 3.5)
VAAP	2.0 (−1.0, 4.9)	1.7 (−1.1, 4.5)	−.6 (−3.0, 1.9)
PAAP	3.8 (1.0, 6.5) $P = 0.02$	3.8 (1.2, 6.5) $P = 0.02$	1.5 (−0.8, 3.8)
AI	3.3 (1.4, 5.2) $P = 0.003$	2.8 (0.9, 4.7) $P = 0.01$	1.1 (−0.5, 2.7)
AIR	0.4 (−2.6, 3.3)	0.2 (−2.6, 3.0)	−.5 (−2.9, 1.9)

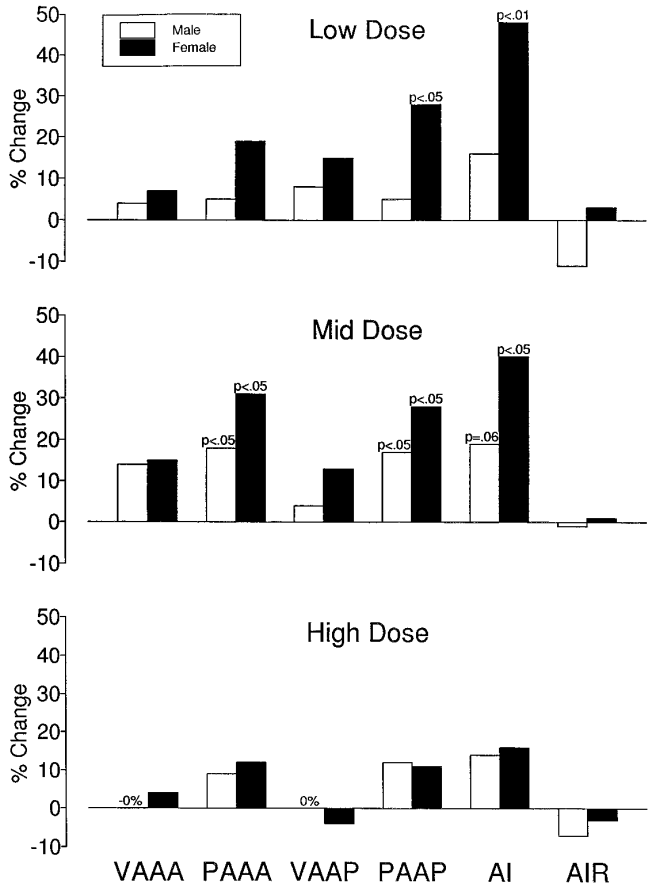

FIG. 1. Percent change in subscale scores for boys (*open bars*) and girls (*solid bars*) at all three dose levels. Significance levels shown represent comparisons of a given treatment level compared with combined placebo scores. See Table 3 for subscale abbreviations.

cents. The scales were originally validated by Olweus *et al.* (30) and Olweus (31) using teacher and peer observations of a group of Swedish schoolboys. Its reliability in other populations (20) and for this study has been confirmed. The absolute aggression scores obtained in our study group were lower than the scores obtained from normative populations, suggesting that sexually delayed subjects are less aggressive than either British adolescents (20) or a nonclinical sample of central Pennsylvania adolescents (our unpublished data). No attempt was made to compare the subject's responses with significant others (parents, teachers, or peers). The degree of agreement between adolescents and these others has been shown to be low (35). There is no other practical method to obtain this information for this longitudinal study. Self-report is widely used and is felt in general to represent accurate reporting.

The current findings indicate strong effects on self-reported aggressive behaviors when estrogen is taken by adolescent girls at very low doses (0.15 mg daily conjugated estrogen). The changes in self-reported aggressive behaviors appeared only at the mid dose (50 mg testosterone) in our study boys. We speculate that the conversion of testosterone to estrogen may be one mechanism involved in causing an increase in hormone-dependent aggressive behavior in boys (36).

Estrogen has recently been shown to play a role in the control of epiphyseal maturation in both sexes (37, 38), effects previously thought to be influenced mainly by testosterone. In addition, in the transgenic, estrogen receptor knockout male mouse there is a marked diminution of aggressive behaviors in animals who would ordinarily be quite aggressive in test situations (39). These data, along with our own, provides support for the notion that estrogen may play a significant role in the production of aggressive behavior in both sexes.

The literature on estrogenic effects on aggression in animals is contradictory, and the data are very limited in humans (32). Inoff-Germain *et al.* (17) found aggressive behaviors by girls towards their parents were related to endogenous androstenedione and estradiol levels. Brooks-Gunn and Warren (11) reported a significant quadratic trend between the concentration of endogenous estradiol and aggressive behavior in a group of teenage girls followed over 1 yr.

Because the largest number of boys in this study had constitutional delay in growth and development, their secretion of endogenous testosterone was monitored during placebo periods. A secondary analysis of data was performed eliminating the aggression data from those boys after the time when their endogenous testosterone concentrations (assessed at the end of placebo periods) exceeded 50 ng/dL. The results for the boys whose endogenous testosterone remained below 50 ng/mL were essentially unchanged. There were significant increases in physical aggressive behaviors

TABLE 6. Median hormone levels attained during study protocol

Gender	Dose period[a]	N	Total Testosterone (ng/dL)[b]	Estrone sulfate (pg/ml)[c]	Urine FSH[d]	Urine LH[e]
Boys	Pre-low	30	18	88	191	253
	Low	28	177	106	50	171
	Pre-mid	32	32	114	197	274
	Mid	32	198	161	59	167
	Pre-hi	30	88	100	242	440
	High	30	398	277	54	154
Girls	Pre-low	12	<15	54	272[e]	737
	Low	13	<12	842	220	199
	Pre-mid	14	<15	107	2901[e]	1353[e]
	Mid	14	<10	1418	141	186
	Pre-hi	14	<17	100	4782[e]	1769[e]
	High	14	<15	2114	54	127

[a] Pre- indicates placebo exposure whereas administered hormone effects are specified by dose as low, mid, or high.
[b] ng/dL × .0347 = nmol/L.
[c] pg/mL × 3.699 = pmol/L.
[d] Prepubertal (urine) FSH < 150 mIU/h; LH < 100 mIU/h.
[e] High levels reflect relatively large number of agonadal girls.

against peers and adults, but not in aggressive impulses all seen only at the mid dose level of treatment.

Our results for the effect of testosterone in boys are in agreement with data for animals and adults (40, 41). Olweus *et al*. (30) and Olweus (31) reported a strong correlation between the concentration of testosterone and responses to the OMAI in a group of 16-yr-old Swedish schoolboys.

The present results also beg further words related to causality in the particularly complex arena of behavioral outcomes. A randomized clinical trial is clearly the optimum study design to demonstrate cause and effect. The epidemiological criteria for causality include the strength, consistency, specificity, temporal order, and the biological plausibility of the relationship and demonstration of a dose-response or duration effect (42). The effects of sex steroids on aggressive behavior scores in this study are strong, with highly significant differences. The results are consistent because both boys and girls responded similarly. There is also a clear temporal sequence in that aggressive behavior scores increased significantly only during hormone administration and not during placebo administration. The results show some increase from the low to middle dose for girls only that could be a dose-response effect, which has been demonstrated for adult men who received increasing doses of testosterone and demonstrated increasingly more aggressive behaviors in a laboratory simulation (43). However the response appears to wane at the high dose, and is more compatible with a threshold effect in which the increases in aggressive behaviors are seen above a certain level of exposure and do not increase further once that level has been achieved. This mechanism has been demonstrated during administration of supraphysiological doses of testosterone to healthy eugonadal men because huge doses of testosterone did not demonstrate an increase in angry behavior (44). The overall effects are clearly plausible and consistent with experiments performed in animals and other reports in the human. This does not mean that social influences have few effects on aggression in youth. Social influences probably have greater explanatory power than the hormonal effects (see *Subjects* effects in Table 3) on changes in aggressive behaviors during adolescence.

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