Anabolic steroids and craniofacial growth in the rat

Roger L. Barrett, DDS, MS; Edward F. Harris, PhD

The misuse of anabolic steroids has received considerable public attention, particularly after the controversy surrounding their use by athletes competing in the 1988 Olympic Games. Abuse is particularly common among athletes[1,2] but frequently is employed by others seeking the cosmetic benefits of enhanced muscle mass.[3,4] Anabolic steroids were first used by Russian athletes in 1954 and American athletes in the late 1950s.[5-7] They are used to increase muscle mass and, thereby, athletic performance – but these changes are not free of side effects. Subadults are at risk of abnormal psychosexual maturation, depression, euphoria, aggressiveness, genitourinary dysfunction, endocrine disturbances, cardiovascular disorders, and dermatological pathologies.[7-12]

Epidemiological studies disclose a significant public health problem with anabolic steroids. A survey of U.S. high schools[13] showed that 7% of male seniors use or had used anabolic steroids, and two-thirds of these initiated use when they were 16 years of age or younger. Primary reasons cited for the abuse were to improve athletic performance and physical appearance. Users are motivated by social influences, knowledge of beneficial effects, and denial of adverse effects.[14] A study of San Antonio high schools found 3% of students had used anabolic steroids,[9] and a survey of Arkansas high schools found that 9% to 19% of eleventh grade males use or had used anabolic steroids.[15] Terney and McLain[16] found that 6.5% of male and 2.5% of female high school students had used steroids. Obviously, the frequency of use among professional body builders

Abstract

Anabolic steroids are misused by adolescents as well as adults to increase muscle mass and improve appearance and athletic performance. Since these substances strongly enhance protein synthesis, it was speculated that craniofacial changes in bone size and, perhaps, skeletodental relationships might also occur. Eighty rat pups were divided into three groups: (1) sham-treated controls, (2) a low-dose group (1 mg/kg/wk nandrolone phenpropionate), and (3) a high-dose group (10 mg/kg/wk). The high-dose regime more closely mimics dosages used by abusers. Steroid therapy significantly increased all measures of the craniofacial complex (k=20)—on the order of 3-5%—except some precocious calvarial dimensions. Importantly, significant alterations also occurred in facial morphology. The low-dose group exhibited proportionate increases in most craniofacial dimensions, but the high-dose produced overt shape changes, notably a maxillomandibular, anteroposterior jaw discrepancy due to maxillary excess. In sum, this anabolic steroid significantly altered facial growth in this animal model; by extension, steroid abuse by adolescent humans may produce discernible changes in their craniofacial complexes.

Key Words

Facial growth • Anabolic steroids • Mandibular retrognathia • Etiology of malocclusion

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Table 1
Craniometric reference points

Basion:	most posterointerior point on the anterior margin of foramen magnum (Ba).
Occipitale:	most posterior point on the external occipital crest (Oc).
Point A:	most posterior extent of the concavity on the anterior aspect of the premaxilla (A).
Point CW:	most medial point on the bony ridge on the lateral aspect of the right and left temporal bone posterior to the zygomatic process.
Point MW:	most lateral extent of the right and left maxillary bone anterior to the zygomatic process.
Point VA:	most superior point on the ectocranial surface of the anterior neurocranium.
Vertex:	most superior point on the ectocranial surface of the posterior neurocranium (Vt).
Point PPP:	most posterior extent of the horizontal process of the palatine bone.
Point ISS:	central point of the intersphenoidal synchondrosis in the midsagittal plane.
Prosthion:	most anterior extent of the maxillary labial alveolar crest in the midsagittal plane (Pr).
Point Mx:	most lateral surface of the right and left maxillary molars at their junction with the maxillary alveolar ridge.
Infradentale:	most anterior extent of the mandibular labial alveolar crest in the midsagittal plane (Id).
Point MMxM:	intersection of the maxillary alveolar crest and mesial surface of the maxillary first molar.
Point DMxM:	intersection of the maxillary alveolar crest and distal surface of the maxillary third molar.
Point MMnM:	intersection of the mandibular alveolar crest and the mesial surface of the mandibular first molar.
Point DMnM:	intersection of the mandibular alveolar crest and the distal surface of the mandibular third molar.
Gonion:	most posterior point on the bony contour of the gonial angle of the mandible (Go).
Condylion:	most posterior-superior point on the mandibular condyle (Co).
Condylion S:	most superior point on the mandibular condyle (CoS).
Point MR:	most inferior aspect of the mandibular body in the region of the masseteric ridge.
Point Cr:	most superior point on the coronoid process of the mandible

is considerably higher (> 50%).[1,17]

The most commonly used parenteral preparations are nandrolone decanoate, nandrolone phenpropionate, testosterone enanthate, and testosterone cypionate. Nandrolone is preferred over testosterone since it can be used in longer-acting weekly or monthly injections with fewer androgenic effects than testosterone.[18,19] Androgen means "producing male-like effects" and is used synonymously with the term "male sex hormone." This term is applied to substances with activity comparable to testosterone. In an attempt to dissociate the androgenic and anabolic effects of testosterone, various synthetic derivatives have been developed. Due to their significant effects on protein metabolism, these are collectively termed anabolic steroids.[20]

Studies have documented the growth-promoting effects of testosterone and various synthetic anabolic steroids on the long bones of children and various animals.[21-27] In contrast, the influence of anabolic steroids on growth of the craniofacial complex has not been investigated. The purpose of the present work was to quantify the effects of nandrolone phenpropionate on growth of the craniofacial complex in the rat. Nandrolone was used because of its current popularity among athletes.

Materials and methods

Ten litters of inbred Sprague-Dawley rats were obtained from Harlan Breeding Laboratories (Indianapolis, Indiana). Each litter consisted of 11 pups. Pups were weighed at 21 days of age; those with aberrant weights (i.e., exceeding 2 SD from the grand mean) were culled. This left at least four male and four female pups of uniform body weight in each litter. Eight from each litter (four of each sex) were then randomly assigned to one of three groups.

Ten male and ten female pups were assigned to a sham-treated control group. These received weekly injections of sterile sesame oil (the drug

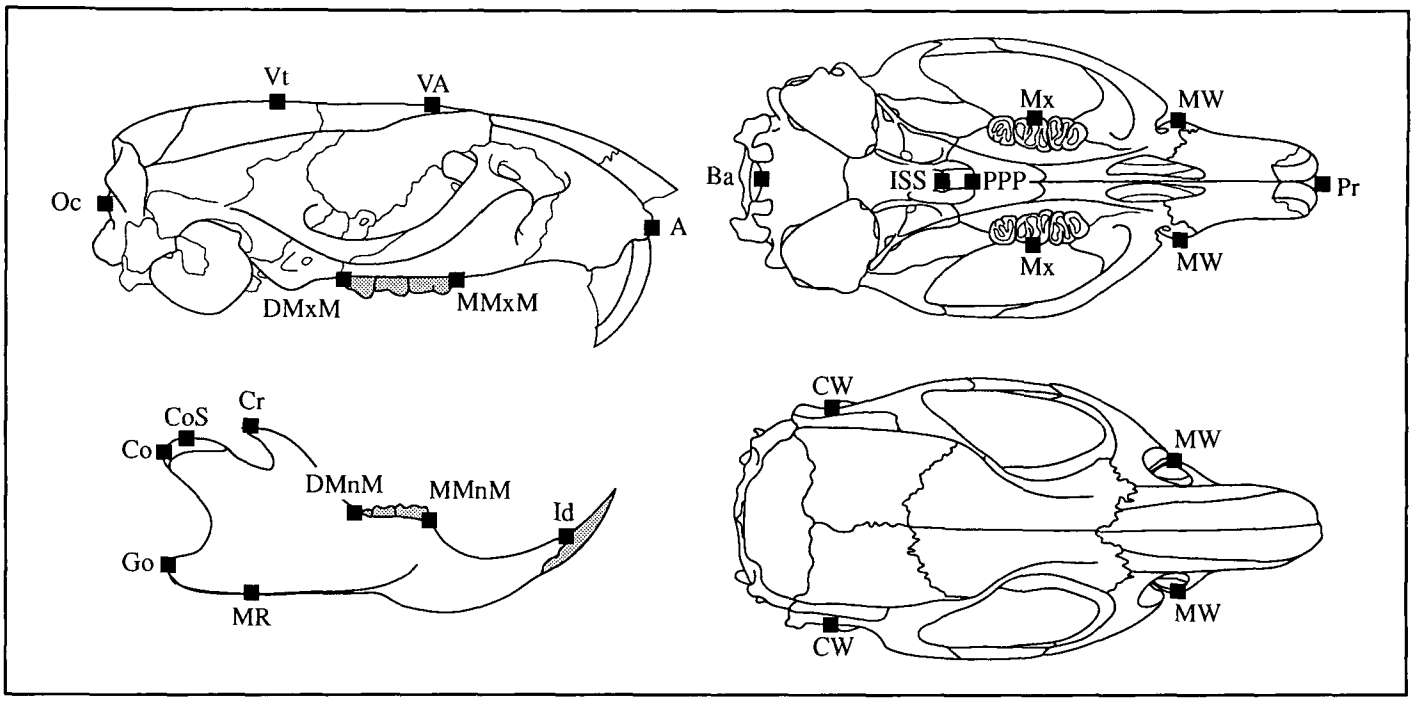

Figure 1

vehicle). Fourteen males and sixteen females were assigned to the first treatment group (T1); these received doses of nandrolone phenpropionate (Durabolin®), 1.0 mg/kg/wk. Sixteen male and fourteen female pups were assigned to the second treatment group (T2) and received doses of 10.0 mg/kg/wk. Injections were subcutaneous over the region of the scapula. With a known dose and elimination rate, plasma concentration was plotted against time, based on a pulsed dosing scheme of one-week intervals. A one-compartment pharmacokinetic model predicted that the plasma concentration would decrease to zero prior to the next injection, so complete clearance was expected within each weekly interval.

Forelimb weight was measured from the intact left and right extremity after skinning, consisting of the scapula and long bones and all attached muscle groups. Attached muscles consisted primarily of the infraspinatus, biceps brachii, triceps brachii, flexor carpi ulnaris, extensor carpi ulnaris, and pronator teres.

Direct millimetric measurements of the skeletodental variables were obtained using electronic sliding dial calipers. The anatomical landmarks (Table 1) are diagrammed in Figure 1. Fourteen linear dimensions were measured on each skull.

Analysis of error

Intraobserver repeatability was assessed by remeasuring 11 randomly selected cases (14% of sample). All measurements were made by one author (RLB), which precluded interobserver differences. The Dahlberg statistic[28] was used:

$$\sqrt{\frac{\Sigma(X_{1i} - X_{2i})^2}{2n}}$$

where X_{1i} and X_{2i} are the pairs of repeated measurements and n is the number of pairs of measurements. The Dahlberg statistic is expressed in millimeters and can be read as the average amount

Table 2
Recognized sources of variation in the type III, mixed-model analysis of variance.

Main Effects (between subjects)
Treatment
Sex
Treatment-x-Sex
Animals within Groups
Interaction Terms (within subjects)
Litter
Treatment-x-Litter
Sex-x-Litter
Treatment-x-Sex-x-Litter
Litter-x-Animals within Groups

Figure 1
Schematics of a rat skull illustrating the location of the craniometric landmarks.

Table 3
Descriptive statistics and results of analysis of variance[A]

Variable	Controls $\bar{x}$	Controls SD	Treatment One[B] $\bar{x}$	Treatment One[B] SD	Treatment Two[B] $\bar{x}$	Treatment Two[B] SD	Analysis of Variance (F-Ratios) Treatment	Sex	Litter	Interaction
Body Weight										
week 3	45.200	2.658	44.929	3.362	44.875	4.660	0.5	11.4*	10.7*	0.5
	43.300	3.860	43.688	2.414	42.571	3.228				
week 9	283.700	9.810	301.357	16.132	274.875	18.522	2.5*	543.8*	2.5	15.0*
	192.700	11.908	239.063	8.903	224.429	13.659				
Forelimb Weight	7.261	0.249	7.776	0.404	7.836	0.643	37.2*	271.5*	2.7*	4.5*
	5.429	0.291	6.639	0.237	6.518	0.435				
Coronoid H	11.751	0.185	12.015	0.267	11.669	0.360	42.1*	100.8*	8.0*	1.5
	11.328	0.288	11.683	0.216	11.089	0.270				
Condylar H	10.712	0.245	11.045	0.266	10.843	0.333	26.2*	162.6*	8.6*	1.8
	10.240	0.259	10.580	0.217	10.196	0.211				
Funct MN L	25.523	0.260	25.812	0.401	25.379	0.672	20.2*	126.4*	6.3*	1.2
	24.461	0.418	25.111	0.413	24.401	0.462				
Mandibular L	25.709	0.301	26.123	0.394	25.868	0.629	18.2*	148.9*	6.0*	1.2
	24.479	0.518	25.328	0.423	24.816	0.478				
Posterior MN L	17.146	0.196	17.438	0.229	17.013	0.372	17.6*	118.7*	1.8	1.0
	16.392	0.263	16.799	0.258	16.504	0.242				
Ramus L	10.779	0.222	10.994	0.265	10.787	0.399	10.2*	67.1*	1.9	0.9
	10.137	0.159	10.587	0.341	10.216	0.339				
Calvarial L	41.885	0.292	42.554	0.415	42.364	0.631	29.5*	240.0*	2.7*	4.8*
	40.194	0.531	41.425	0.352	40.526	0.540				
Calvarial W	15.181	0.226	15.246	0.297	15.094	0.356	3.5	56.8*	2.5	0.0
	14.735	0.243	14.823	0.262	14.628	0.190				
Calvarial H	10.255	0.188	10.375	0.129	10.254	0.180	14.1*	127.8*	5.6*	0.6
	9.886	0.102	10.094	0.139	9.913	0.192				
Cranial Base L	13.622	0.195	13.980	0.281	13.777	0.359	18.1*	98.5*	3.0*	0.4
	13.033	0.217	13.488	0.248	13.211	0.225				
Midfacial L	24.408	0.191	24.701	0.250	24.737	0.387	21.9*	235.3*	2.8*	6.0*
	23.234	0.334	24.017	0.252	23.616	0.377				
Midfacial W	8.529	0.156	8.777	0.128	8.735	0.242	24.1*	100.7*	1.9	1.6
	8.040	0.148	8.474	0.167	8.320	0.197				
Midfacial H	10.209	0.126	10.376	0.179	10.349	0.208	21.9*	186.6*	3.3*	3.3
	9.645	0.157	10.047	0.127	9.849	0.182				
MX Arch W	8.301	0.125	8.406	0.225	8.244	0.209	9.0*	31.9*	4.0*	1.8
	7.986	0.235	8.244	0.131	8.136	0.183				
MN Arch L	14.744	0.212	14.819	0.221	14.592	0.425	11.9*	56.7*	7.7*	0.3
	14.324	0.353	14.523	0.268	14.185	0.258				
FL Wt / Body Wt	0.050	0.000	0.050	0.000	0.058	0.004	23.4*	48.30*	0.8	3.1
	0.058	0.004	0.056	0.005	0.061	0.003				
Cd H / F MN L	0.420	0.007	0.429	0.009	0.428	0.010	4.3*	12.2*	1.5	1.4
	0.418	0.008	0.423	0.006	0.418	0.007				
MFL / MN A L	1.656	0.024	1.667	0.019	1.696	0.030	17.2*	19.9*	4.2*	1.9
	1.623	0.027	1.654	0.035	1.665	0.031				
MFL / F MN L	0.956	0.011	0.956	0.010	0.976	0.016	21.4*	2.2	3.3*	1.4
	0.948	0.011	0.956	0.012	0.968	0.017				
MFW / MFL	0.349	0.007	0.356	0.006	0.353	0.008	6.4*	0.6	1.5	0.6
	0.346	0.008	0.354	0.007	0.353	0.010				
MFH / MFL	0.418	0.004	0.420	0.006	0.417	0.006	1.2	2.2	1.2	0.3
	0.415	0.007	0.418	0.007	0.417	0.007				

Abbreviations are: Height (H), Length (L), Width (W), Weight (Wt, gms), Forelimb (FL), Maxillary (MX), Mandibular (MN), Condylar (Cd), Midfacial Length (MFL), Midfacial Width (MFW). Linear measurements are in mm.

[A]Statistics for males are listed first, then females

[B]Treatment One = 1.0 mg/kg/wk; Treatment Two = 10.0 mg/kg/wk

*$P < 0.01$

of disparity between the measurement sessions.[29,30] Intraobserver error was less than 0.1 mm for all variables.

Statistical analysis

The primary statistical design was three-way analysis of variance.[31,32] This was a mixed model (Model III). Main effects were treatment, gender, litter (Table 2). Treatment and gender were fixed effects. Litter (a random effect) was included to control for the intrinsic variability among litters in size and patterns of growth. Preliminary analyses used this full ANOVA model. But, because of the nature of the experiment, treatment-x-litter, sex-x-litter, and the second-order term (T-x-S-x-L) were quite unlikely to achieve significance since these three sources of variation were controlled by the experimental design. To simplify presentation and ignore trivial terms, a reduced model was used. Variation in the three deleted terms becomes part of the residual term, but the reduced model is much simpler to present, and the residual mean squares is the appropriate denominator for computation of the four F-ratios. This reduced model was computed using the PROC GLM (generalized linear model) algorithm.[33] All tests of significance were two-tailed. Given the large sample sizes and proportionate cell sizes, the alpha level was set at 0.01 for the claim of statistical significance rather than the traditional 0.05.

Results

The myotrophic effect of nandrolone was obvious (Table 3). Body weight increased on the order of 9% relative to controls, and forelimb weight (essentially a measure of muscle mass) was 13% greater. Statistically, the single source of significance was between controls and the two treated groups (C < T1 = T2).

Mandibular dimensions

Six measurements were made on the mandible, and all six exhibited highly significant intergroup differences. The nature of the difference was the same throughout (Table 3): The low-dose group was significantly larger than controls or the high-dose group (C = T2 < T1). Since the size and position of most of the mandibular landmarks are influenced by the function of the muscles of mastication, differences may reflect the myotrophic influence of the steroid.

Calvarial size

Anteroposterior growth of the calvaria was significantly affected by steroid treatment, though not in a dose-dependent fashion and differently in the two sexes. The significant treatment-by-sex interaction was due to different responses of the

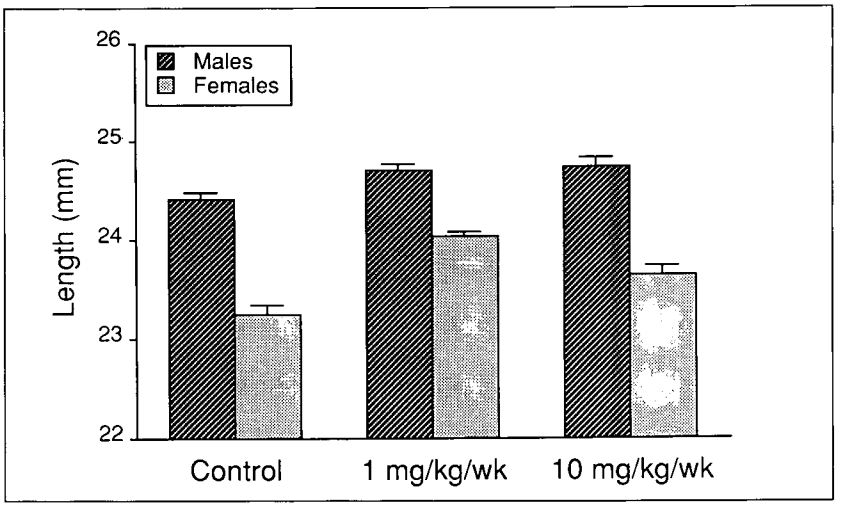

Figure 2

T2 series. In males, the T2 mean was only slightly less than that of the low-dose group, so the statistical relationship was C < T1 = T2. In females, the T2 group grew much less than the low-dose series, and it aligned instead with controls, C = T2 < T1. Calvarial height displayed the common pattern of intergroup differences: C = T2 < T1. Again, the effect of the steroid in low dose was to significantly enhance bone growth (by 2% relative to controls), and there was no growth advantage with the higher dose.

Cranial base

The commonly encountered pattern of intergroup differences (C = T2 < T1) also occurred for cranial base length. The low-dose average was 3% greater than controls. This variable, which measures endochondral rather than intramembranous bone growth, also exhibited significant sex dimorphism; the cranial base length was 4% longer in males than females.

Midface

There was a highly significant interaction for midfacial length (Figure 2). Females responded more to the steroid than males, and, in females, the high-dose average for this dimension was intermediate between controls and the T1 group. This led to all three groups of females being significantly different from one another (C < T2 < T1). Group differences were not significant for males. Midfacial width responded differently among the three series. Here, both treated groups had widths significantly greater than controls (i.e., C < T1 = T2). Not only did the T1 series exhibit midfacial widths which were, on average, 4% greater than controls, but the midfacial widths of the T2 series were 3% greater than controls. Midfacial height was significantly greater in the T1 series than the T2 group and controls. These three variables

Figure 2
Bar chart of average (± SEM) midfacial lengths (PPP to Pr). In both sexes (but particularly in females), the two treated groups have longer midfacial lengths than controls.

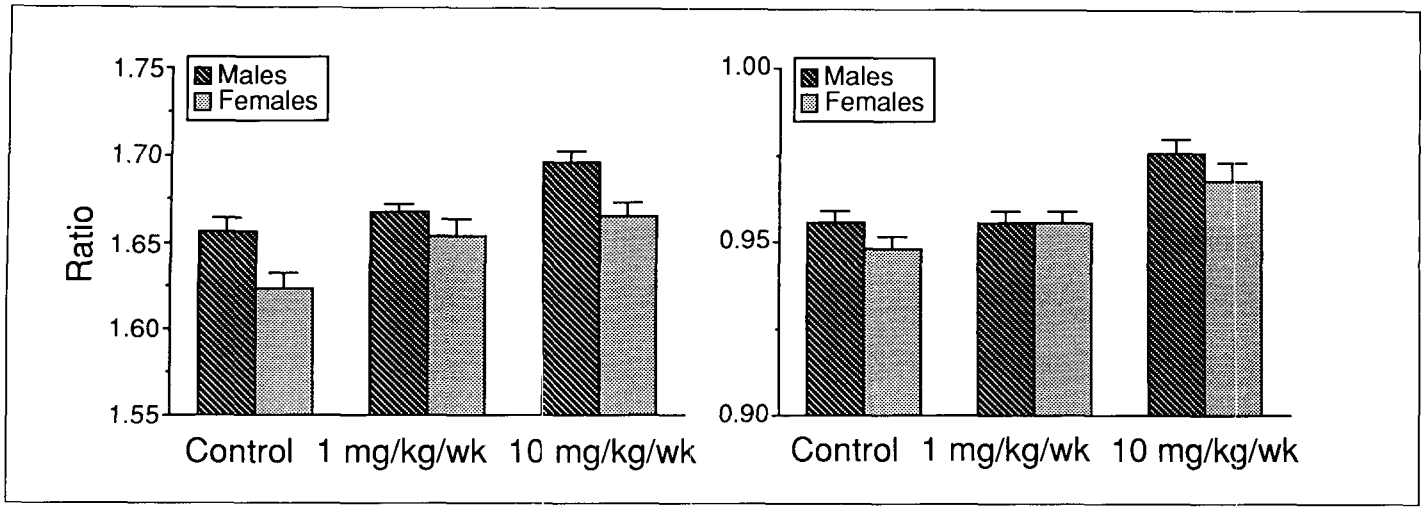

Figure 3

Figure 3
Bar charts of the two ratios used to assess maxillomandibular relationships: (left) midfacial length divided by mandibular arch length (PPP-Pr/Go-Id) and (right) midfacial length divided by functional mandibular length (PPP-Pr/Co-Id). In both instances, the high-dose group had a significantly higher ratio due to the midface being longer relative to mandibular length. In humans, this would be termed a Class II skeletal relationship resulting from excessive midfacial growth. As shown in Figure 2, this difference is due to overgrowth of the maxilla; mandibular lengths (Go-Id and Co-Id) did not grow significantly more in the T2 groups than controls (Table 3). Consequently, the steroid produced both size and shape differences in the craniofacial complexes.

show that steroid therapy influenced growth of the midface in the vertical, transverse, and anteroposterior planes.

Low-dose treatment significantly increased transverse development of the maxillary dental arch (C = T2 < T1). The low-dose group was, on average, 2% broader than controls. Significant intergroup differences also occurred in mandibular arch length, with the recurrent relationship, C = T2 < T1.

Differences in proportionality

Four ratios were selected as of particular interest regarding the presumed myotrophic influence of anabolic steroids and to more clearly investigate cranial shape with ratios developed along the lines of classic craniometry.[34]

Condylar height to functional mandibular length. This ratio (MR-CoS/Co-Id) assessed mandibular growth in the vertical versus the anteroposterior plane. There was no difference among groups; by this measure, shape of the mandible was unaffected, though overall size increased appreciably.

Ramus length to mandibular arch length. To test for possible disproportionate growth stimulation in different regions within the mandible, the length of the ramus was compared to the length of just the tooth-bearing portion of the mandible (Co-DMnM/Go-Id). There was no difference among groups, though the gender difference was significant because of the larger ramus relative to the length of the corpus in males, reflecting a more robust morphology.

Midfacial length to mandibular arch length. Midfacial length and mandibular arch length are measures of the anteroposterior dimension of tooth-bearing osseous structures in the maxilla and mandible, respectively (Figure 3). The value of this ratio (PPP-Pr/Go-Id) was equivalent in the T1 and control series. That is, the T1 series exhibited proportionate growth in the tooth-bearing structures of the two jaws (in the anteroposterior plane) although the amount of growth was much greater than in controls. This ratio was significantly greater in the T2 series. Scrutiny of the individual variables disclosed that this "Class II" tendency was a result of maxillary protrusion rather than of mandibular deficiency.

Midfacial length to functional mandibular length. This ratio (like that just described) tested for differences in the AP relationship of the supporting structures of the upper and lower dentitions (PPP-Pr/DMnM-Id). The ratio was significantly larger in the T2 group (C = T1 < T2). High-dose animals experienced disproportionately more growth in midfacial length than mandibular length (Figure 3). There was a significant change in craniofacial morphology. The T2 series exhibited an anteroposterior discrepancy, with maxillary protrusion and ***relative*** mandibular deficiency.

Discussion

Nandrolone phenpropionate significantly altered growth of the craniofacial complexes. Importantly, this drug produced significant alterations in craniofacial size and shape.

Recent epidemiologic studies[9,13,15,16] show that the medically unsupervised use of anabolic steroids is a significant public health concern that has been underestimated and unappreciated by many health authorities. As the significance of this problem becomes more evident,[12,35,36] controlled studies on the effects of anabolic steroids on various organs and structures are increasingly relevant. The focus of the present study was on whether an anabolic steroid had any discernible effect on bone growth in the skull – with the per-

spective that changes might be extrapolated to potential problems in humans. Estimates of anabolic steroid abuse in adolescents are on the order of 5% to 10%, but, to our knowledge, this is the first study to address whether these potent enhancers of protein synthesis produce skeletodental effects.

The two dosages used here are informative for a variety of reasons. First, the lower dose, 1 mg/kg/wk, is in the therapeutic range for this particular anabolic steroid in humans. Justification for the use of the higher dosage regimen, 10 mg/kg/wk, focused on disclosing a significant dose-dependent response if, in fact, one exists. Any significant influence on craniofacial growth and development, even at supra-therapeutic but realistic dosages, would be informative. Thirdly, the higher dosage regimen more closely mimics those by individuals in medically unsupervised settings.[1,16,17,37]

The manner of steroid use by athletes is quite different from that prescribed medically. Users commonly "stack", "pyramid", or "stagger" drugs, hoping to gain a greater effect.[38] "Stacking" is the use of multiple drugs at the same time, commonly an injectable form and one or more oral preparations. "Pyramiding" begins with small doses of one or more drugs, increasing the dosages in the following weeks until a predetermined maximum is reached. Thereafter, decreasing dosages are taken. "Staggering" means using one drug until no further improvement is evident, then switching to a more potent steroid while tapering off the previous drug.

Forelimbs (muscle mass)

Based on forelimb weight, nandrolone phenpropionate had a profound, dose-related influence on the development of muscle mass. The anabolic effect was evident in both sexes but more dramatic in females. This may reflect the lower levels of endogenous androgens in females.[39-41] Rahwan[10] has suggested that in female athletes androgens and anabolic steroids increase muscle mass more than in males because the higher level of endogenous testosterone naturally present in males is already producing near-maximum anabolism. So, a greater response in females should be anticipated since endogenous levels of testosterone are much lower. Also, Rahwan reported that the erythropoetic effect of androgens and anabolic steroids is not observed in non-anemic males because the higher levels of endogenous testosterone are already achieving maximal erythropoesis.

Craniofacial morphology

Possibly the most important findings of this study—from an orthodontic perspective—center on the influence of the drug on jaw lengths. While the T1 series exhibited significant increases in the linear growth of midfacial length and mandible, growth was proportionate. Facial dimensions increased significantly in all three planes of space, but the skeletodental relationship remained the same; the low-dose animals were "scaled-up" versions of the controls. This is what Moyers et al.[42] term "maintenance of pattern". In contrast, the T2 series exhibited a disproportionate increase in midfacial and mandibular length because the midface grew relatively more than the mandible. Extrapolated to humans, this maxillomandibular disharmony would be a skeletal "Class II" condition due to maxillary protrusion.[43,44]

Treatment with the higher dose significantly altered the maxillomandibular skeletal relationship. This is confirmed by inspection of two ratios, (1) midfacial length to mandibular arch length and (2) midfacial length to functional mandibular length. In humans, mandibular length is about 120 mm in adult females and 130 mm in adult males.[45] A 4% increase in mandibular length in the human adult would amount to a 4 mm increase. Although not insurmountable, an anteroposterior discrepancy of 4 mm is a substantial orthodontic challenge to achieve harmonious dental, skeletal, and soft tissue relationships.

Age at treatment

We purposely blanketed much of the postnatal period of active growth because there has been no research in this area, and, as a first step, it was important to learn whether craniofacial structures could be affected at all. Further investigations are needed to determine whether shorter and more selective intervals of treatment produce different results depending on the stage of development. For example, midfacial growth is usually completed earlier than mandibular growth in humans.[46-49] Therefore, if anabolic therapy coincides with the active period of midfacial growth, maxillary protrusion could be enhanced. Likewise, if therapy is initiated later, but while mandibular growth is still active, lower jaw growth might be enhanced. Anabolic steroids enhance protein synthesis systemically; drug treatment may simply augment the growth of actively growing structures, whatever they may be.

Another, indirect mechanism contributes to the observed changes in morphology. Since form is influenced by function,[50-55] the change in osseous morphology of the mandible may, in part, result from greater functional forces of the larger muscles developed by steroid treatment. Larger masseter, temporalis, and internal pterygoid muscles would induce appositional growth at the origins and insertions of these muscles.[56,57]

The small differences in calvarial width and height support this theory. These dimensions depend on the development of the neural mass, and neural development is precocious compared to somatic and skeletal development.[58,59] Since neural growth was essentially complete by the time treatment was initiated, only minimal differences were seen between the control and treated groups.

Conclusions

This study quantified the effects of a commonly-abused anabolic steroid, nandrolone phenpropionate, on development of the craniofacial complex in the white rat. Since anabolic steroids strongly enhance protein synthesis, it seemed likely that all actively growing tissues would be affected to some extent, not just the intended enhancement of muscle mass.

1. Nandrolone phenpropionate significantly influenced the growth of the craniofacial complexes, resulting in significant alterations in size and morphology.

2. Females were more sensitive to this agent than males, presumably because of the absence of substantive levels of endogenous androgenic hormones, notably testosterone.

3. The lower dosage (1 mg/kg/wk) produced greater dimensional changes in the skull than the higher dose (10 mg/kg/wk). The low-dose is near the middle of the therapeutic range for humans. The high dose exceeds the therapeutic range, but it approximates the misuse of this substance which involves the "stacking" and "pyramiding" of drugs.

4. Of particular interest, the high dose produced overt changes in craniofacial morphology, notably a maxillomandibular, anteroposterior jaw discrepancy.

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Author Address

Dr. Edward F. Harris
Department of Orthodontics
College of Dentistry
University of Tennessee
875 Union Avenue
Memphis, Tennessee 38163

R. L. Barrett is in private practice in Poteau, Oklahoma. This paper is based on his research for the degree of Master of Science in Orthodontics and Dentofacial Orthopedics, University of Tennessee, Memphis. Dr. Barrett's thesis received an Award of Special Merit from the American Association of Orthodontists, 1992.

E. F. Harris is Professor in the Department of Orthodontics and the Department of Pediatric Dentistry, University of Tennessee, Memphis.

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