Estrogen and Testosterone, But Not a Nonaromatizable Androgen, Direct Network Integration of the Hypothalamo-Somatotrope (Growth Hormone)-Insulin-Like Growth Factor I Axis in the Human: Evidence from Pubertal Pathophysiology and Sex-Steroid Hormone Replacement*

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ABSTRACT

Activation of the gonadotropic and somatotropic axes in puberty is marked by striking amplification of pulsatile neurohormone secretion. In addition, each axis, as a whole, constitutes a regulated network whose feedback relationships are likely to manifest important changes at the time of puberty. Here, we use the regularity statistic, approximate entropy (ApEn), to assess feedback activity within the somatotropic (hypothalamo-pituitary/GH-insulin-like growth factor I) axis indirectly. To this end, we studied pubertal boys and prepubertal girls or boys with sex-steroid hormone deficiency treated short-term with estrogen, testosterone, or a nonaromatizable androgen in a total of 3 paradigms. First, we cross-sectional analysis of 53 boys at various stages of puberty or youth adulthood revealed that mean ApEn, taken as a measure of feedback complexity, of 24-h serum GH concentrations profiles is maximal in pre- and mid-late puberty, followed by a significant decline in postpubertal adolescence and young adulthood (P = 0.0008 by ANOVA). This indicates that marked disorderliness of the GH release process occurs in mid-late puberty at or near the time of peak growth velocity, with a return to maximal orderliness thereafter at reproductive maturity. Second, oral administration of ethinyl estradiol for 5 weeks to 7 prepubertal girls with Turner’s syndrome also augmented ApEn significantly (P = 0.018), thus showing that estrogen per se can induce greater irregularity of GH secretion. Third, in 5 boys with constitutionally delayed puberty, oral testosterone administration also significantly increased ApEn of 24-h GH time series (P = 0.0045). In counterpoint, 5 α-dihydrotestosterone, a nonaromatizable androgen, failed to produce a significant ApEn increase (P > 0.43). We conclude from these three distinct experimental contexts that aromatization of testosterone to estrogen in boys, or estrogen itself in girls, is likely the proximate sex-steroid stimulus amplifying secretory activity of the GH axis in puberty. In addition, based on inferences derived from mathematical models that mechanistically link increased disorderliness (higher ApEn) to network changes, we suggest that sex-steroid hormones in normal puberty modulate feedback within, and hence network function of, the hypothalamo-pituitary/GH-insulin-like growth factor I axis. (J Clin Endocrinol Metab 82: 3414–3420, 1997)
network control is mediated via SRIH and GHRH of hypothalamic origin, GH of pituitary origin, and IGF-I and its binding proteins produced in various target tissues. Investigation of changes in such in vitro networks is difficult.

As an indirect estimate of feedback control within an axis, approximate entropy (ApEn) has been applied in a variety of mathematical and biological settings, such as aging, tumoral hormone secretion, feedback withdrawal, and gender-specific patterns of hormone secretion (17–25). For example, ApEn quantifies greater disorderliness of GH release over time in the female than male in both the human and rat (24). In addition, ApEn measures show the disorderliness of GH, LH, and testosterone release increases during healthy aging in adults (19, 25). ApEn, as a measure of regularity, also reveals marked disruption of the orderliness of ACTH, GH, and aldosterone release in Cushing’s disease, acromegaly, and aldosteronoma, respectively (17, 18, 20). Consequently, ApEn offers a discriminative tool with which to assess the loss of coordinated regulation of neurohormone release.

Theoretically, ApEn provides an overall index of feedback behavior in quite a variety of well-determined networks (26–30). The ApEn metric has good statistical replicability in evaluating both dominant (pulsatile) and subordinate (non-pulsatile) features of hormone release over time (31, 32). Thus, ApEn can be used to infer changes in network function; e.g., feedback among the hypothalamus, pituitary gland, and target organ. This is significant, because the feedback activity of endocrine axes cannot be measured directly in clinical experiments.

Given the above framework, we have used ApEn here to test the clinical hypotheses that feedback regulation of the human SRIH/GHRH-somatotropic (GH)-IGF-I axis is altered during normal human puberty and that such altered regulation is effected via one or more specific sex-steroid hormones. To this end, we used three experimental paradigms, namely: 1) a cross-sectional evaluation of 24-h serum GH concentration profiles in 53 boys and young men stratified into 5 groups defined by prepuberty, early puberty, mid-late puberty, postpuberty, and adulthood (33); 2) short-term sex-steroid hormone (estrogen) treatment of 7 prepubertal girls with gonadal dysgenesis (Turner’s syndrome) (34) to test the impact of estrogen on feedback control of GH release; and 3) 5 androgen-deficient boys with constitutionally delayed puberty studied both at baseline and after im administration of testosterone, as an aromatizable androgen, and 5 α-dihydrotestosterone (DHT), as a nonaromatizable androgen (35). We hypothesized that estrogen and testosterone, but not a nonaromatizable androgen, would govern the orderliness of the GH release process, and hence, by inference, modulate feedback regulation of the hypothalamo-somatotroph-IGF-I axis.

Materials and Methods

Clinical protocols

Cross-sectional studies of boys at different stages of puberty. The normal boys studied here were described in an earlier analysis of their pulsatile GH data, which we now evaluate for the first time by way of ApEn measures (33). Fifty-three healthy boys were studied, 10 in prepuberty as defined by Tanner Stage I, 12 in early puberty (Tanner Stage II), and 16 in mid-to-late puberty (defined as pubic hair development in Tanner Stages III and V, but clearly unfused epiphyses on hand x-ray). In addition, 8 boys were tested in early postpuberty as defined by characteristic ages less than 18 with fused epiphyses and typical Tanner Stage V; and, lastly, 7 subjects were recruited in young adulthood, defined as reproducitively mature and 21–30 yr old. All volunteers underwent blood sampling at 20-min intervals for 24 h on 1 occasion each. Serum GH concentrations were assayed in duplicate by immunoradiometric assay (IRMA) (33).

Girls with Turner’s syndrome. Seven untreated prepubertal girls with Turner’s syndrome underwent blood sampling at baseline and after 1 week and 5 weeks of daily oral ethinyl estradiol (100 mg/kg) treatment. Blood was sampled at 20-min intervals from 2000 h to 0800 h overnight and submitted to GH IRMA. GH pulse analysis was reported earlier for these subjects (34).

Boys with constitutional delay of puberty. Five boys with clinically defined constitutional delay of puberty were recruited from the outpatient clinic and studied 4 times each; namely, at baseline; 7 days after an im testosterone enanthate (80 mg, Delatestryl, Gynex Pharmaceuticals, Inc.) injection; at second baseline; and lastly, 7 days after DHT enanthate (80 mg) im. Admissions were spaced at least 5 weeks apart. Androgen injections were randomly ordered. Volunteers underwent 12-h overnight (2000–0800 h) blood sampling at 10-min intervals during each admission. Prestudy testing showed morning concentrations of plasma IGF-I, and serum T4, TSH, (prepubertal) LH and FSH, all of which were normal for bone age, as well as normal biochemical indices of metabolic, hematological, renal, and hepatic function. History and physical examination were unremarkable except for a (mean ± SEM) chronological age of 15.5 ± 0.4 yr, bone age of 12.8 ± 0.4 yr, height z-score of −2.2 ± 0.2 for chronologic age and −0.1 ± 0.2 for bone age, testes vol of 3–5 mL, pubic hair Tanner stages I-II, and a.m. serum total testosterone concentrations of 94 ± 39 ng/dL (3.3 ± 1.4 nmol/L). Volunteers participated with their assent, and after informed consent was obtained from their parents, as approved by the IRB of the University of Virginia. These boys’ data have not been presented previously.

ApEn calculations

ApEn is a model-independent regularity statistic developed to quantify the orderliness of sequential measures (26, 36), such as hormonal time series. Larger ApEn values correspond to greater randomness (irregularity). Technically, ApEn measures the logarithmic likelihood that runs of patterns that are similar remain so on next incremental comparison. The basic derivation and calculation of ApEn have been presented earlier (29, 32). Two input parameters, m (window length) and r (tolerance), must be specified to compute ApEn. For this study, we calculated ApEn values for each GH profile with window length m = 1, and tolerance parameter r = 20% of the average sd of the individual subject’s GH time-series. Thus, this calculated ApEn is denoted as ApEn (1.20%). Previous theoretical analyses and clinical applications have demonstrated that these input values produce good statistical validity of ApEn for time series of 50 or more data points (18, 24, 28, 29). Mathematically stated, the ApEn application with m = 1 is said to estimate the rate of entropy for a first-order (m = 1) approximating Markov chain to the underlying true process (37).

In choosing the r input parameter (tolerance) in ApEn as a fixed percentage of each data set’s sd, we normalize ApEn for each profile. This so-called normalized ApEn is both translation and scale invariant (adding to or multiplying each data value in the hormone profile by a constant would produce an identical ApEn value) (32). This point is important when different absolute hormone levels are expected, as they are here.

ApEn is stable to small changes in noise characteristics and infrequent, albeit significant, outliers (26, 28). This statistic evaluates a variety of dominant and subordinate patterns in the data; for example, ApEn can detect and quantify changes in underlying regularity of hormone release that are not necessarily reflected in changes in peak frequency or amplitude (28). Additionally, ApEn provides a barometer of feedback changes in many coupled systems (28, 30).

ApEn is a family of statistics which individually provides a relative, not absolute, measure of process regularity. ApEn thus can show significant variation in absolute value with changing m or r input parameters, N (data series length), and/or noise characteristics (experimental
Because ApEn will generally increase with increasing N and noise (and hence, increasing intrasay coefficients of variation), it is important to compare data sets with similar N and assay CV’s, as we do here. Technical and statistical properties of ApEn, including so-called mesh interplay, relative consistency of (m, r) pair choices, asymptotic normality under general assumptions, statistical bias, and error estimation for general processes are discussed elsewhere (38).

**Deconvolution analysis**

The serum GH time series were deconvolved, as described earlier (39, 40).

**Statistical analysis**

One-way ANOVA, followed by Duncan’s multiple comparison test, was used to evaluate the null hypothesis that mean ApEn measures of the 24-h serum GH concentration time series are statistically unrelated to pubertal stage across the five study groups (prepuberty, early and mid-late puberty, postpuberty, and adulthood). Similar comparisons were made among mean ApEn values in the prepubertal girls with Turner’s syndrome (treated for 1 or 5 weeks with estradiol), as well as in boys with constitutional pubertal delay (treated with DHT or testosterone). In the latter study, because the two baseline sets of ApEn values were statistically indistinguishable (by paired Student’s t test), they were combined.

**Results**

As summarized in Fig. 1, mean ApEn measures of 24-h serum GH concentration profiles in boys studied cross-sectionally at various stages of puberty showed a maximal absolute value (denoting highest pattern irregularity) in mid-late puberty, and minimum values (greatest ordinariness, or least irregularity) in postpuberty and adulthood (P = 0.0008). ApEn values in the individual boy’s GH time series were quite well determined statistically, because randomly varying the apparent sample GH concentrations within each time series by Monte Carlo simulations (300 realizations/series) with Gaussian variability matching the intrasample sd of the GH assay yielded coefficients of variation of ApEn of approximately 7–13% for any given GH profile (absolute ApEn \(SD \approx 0.05–0.12\)). The lowest ApEn value for the boys and men studied here occurred in young adulthood and was approximately one-half that seen in mid-late puberty. Thus, the difference in the relative ordinariness of GH release between adulthood and puberty was large, namely approximately 4–5 sd’s of individual ApEn values.

In clinical experiments, prepubertal girls with Turner’s syndrome (\(N = 7\)) were treated with oral ethinyl estradiol (100 ng/kg-day) for 1 and 5 weeks. Compared with pretreatment baseline, estradiol induced an increase in GH ApEn and, hence, greater disorderliness of GH release (P for overall treatment effect = 0.018). Baseline ApEn values before estrogen treatment averaged 0.636 ± 0.070, and increased to 0.803 ± 0.043 during short-term estrogen (1 week) replacement (P = not significant), and to 0.849 ± 0.028 during long-term (5 weeks) estrogen replacement; see Fig. 2 for comparison of the latter vs. baseline within-subject values. In this study, absolute ApEn values reflected overnight blood sampling, and thus (although validly compared within and between subjects in this substudy) should not be directly related in absolute terms to 24-h data (pubertal boys, above).

In a second set of clinical experiments comprising five boys with constitutional delay of puberty, basal GH ApEn values at study entry averaged 0.63 ± 0.02 for 12-h GH profiles. Mean ApEn did not change when the baseline sampling was repeated; namely, the repeat ApEn was 0.64 ± 0.03. In addition, DHT enanthate injections did not significantly alter ApEn, the mean value of which was 0.69 ± 0.10 (\(P > 0.43\)). In contrast, testosterone enanthate administration increased mean GH ApEn significantly to 0.87 ± 0.04 (\(P = 0.0045\)); see individual data in Fig. 3. The corresponding mean (12-h) serum GH concentrations (\(\mu g/L\)) were 2.5 ± 0.41 (baseline 1), 3.2 ± 0.82 (baseline 2), 2.3 ± 0.54 (DHT), and 4.9 ± 1.0 (testosterone, \(P < 0.05\) vs. DHT). Testosterone, but not DHT, increased plasma IGF-I and GH deconvolution-calculated

![Fig. 1. ApEn quantification of the orderliness or pattern regularity within 24-h serum GH concentration time series (measured by IRMA) obtained in a total of 53 boys and young men sampled every 20 min for 24 h (33)]. A scale-invariant and model-free statistic, normalized ApEn (1,20%), was calculated here at an \(m\) (window length) value of 1 and an \(r\) (tolerance) value of 20% of the sd of each subject’s GH series (28, 31). Higher ApEn values denote greater disorderliness or irregularity of GH release over time (26). By ANOVA and Duncan’s multiple-comparison test, significant group mean differences are denoted by nonidentical alphabetic superscripts (\(P = 0.008\)). Mean ± SEM ApEn values are given in parentheses below the individual boy’s data.

![Fig. 2. Individual ApEn values of serum GH concentration profiles in seven prepubertal girls with gonadal dysgenesis at baseline (untreated) and after treatment for 5 weeks with oral ethinyl estradiol (100 ng/kg daily)]. Serum GH concentrations were measured by IRMA in blood samples collected at 20-min intervals overnight (34). Estrogen treatment increased ApEn values, which implies greater disorderliness of GH release.

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secretory rates ($P < 0.01$). An illustrative set of four individual 12-h serum GH concentration profiles and their calculated secretion rates and ApEn values are shown in Fig. 4.

**Discussion**

The present clinical studies indicate that a scale-invariant and model-independent statistical measure of the irregularity or disorderliness of 24-h GH release, namely, ApEn, is significantly higher during mid-to-late puberty, compared with adulthood. Because ApEn, when normalized, is uninfluenced by absolute serum GH concentrations, which rise in puberty (33), higher normalized ApEn values in midpuberty (vs. young adulthood) indicate a more disorderly GH release process in midpuberty. In addition, the higher GH ApEn values at the time of puberal growth suggest significantly decreased feedback coordination within the hypothalamosomatotrope-IGF-I axis (below). Further, our clinical experiments in prepubertal (Turner’s) girls showed that treatment with a small dose of ethinyl estradiol (100 ng/kg-day) orally for 5 weeks increases GH ApEn significantly. This rise in ApEn mimics the higher GH ApEn values observed cross-sectionally in mid-late puberty in actively growing boys (higher ApEn), compared with young adults (lower ApEn). Increased ApEn in response to estradiol treatment in girls was emulated by short-term testosterone administration to clinically prepubertal boys with constitutionally delayed adolescence, but notably not by treatment with a nonaromatizable androgen, DHT. Of note in these two (testosterone and estradiol) studies, GH ApEn values consistently increased in each subject, with only a single instance of ApEn decrease in the two studies combined.

In the broadest interpretation of these clinical data, we can postulate that estradiol, or testosterone presumptively acting after its aromatization to estradiol, not only augments the amount of GH secreted but also regulates the feedback control of GH release during puberty and young adulthood, as reflected statistically by scale-invariant ApEn.

One mechanistic hypothesis is that greater regularity (lower ApEn) of hormone release corresponds to greater subsystem autonomy. For the GH axis, subsystems of control are likely represented by hypothalamic regulatory signals (e.g. GHRH, SRIH, etc.), the pituitary somatotropes, GH itself, and the IGF-I (and its binding protein) system. This general hypothesis has been explored theoretically via analyses of several very different (stochastic and deterministic) mathematical models, which established a robustness of the hypothesis (28, 30). Stated technically, ApEn (or relative disorderliness) typically increases with greater within-system coupling, accelerated positive feedback, and greater external influences, at least as inferred from analyses of coupled stochastic differential equations (30), several composite oscillator-noise models, e.g. Refs. 26 and 30, and stochastic control systems or queuing networks. According to such analyses, the present clinical instances of increased disorderliness or irregularity of GH release would indicate a more complex network directing GH secretion. Higher complexity could reflect more critical interacting factors within the GH feedback axis and/or a greater intensity of particular interactions, e.g. among GHRH-SRIH-GH-IGF-I.

The demonstration of greater disorderliness of GH release in midpuberty, compared with young adulthood, and the ability to reproduce such ApEn differences qualitatively by treatment with estrogen or aromatizable androgen, further suggests to us that estrogen per se critically controls feedback (or network) activity within the hypothalamic-pituitary-IGF-I axis in the human. The fact that plasma GH and IGF-I concentrations rise together in the sex-steroid-rich milieu of puberty (41) is consistent with a corollary hypothesis of decreased sensitivity of the hypothalamic-pituitary/GH unit to IGF-I's negative-feedback actions during puberty. Concurrent elevations in plasma GH and IGF-I concentrations otherwise arise only in acromegaly, wherein tumoral GH hypersecretion is less sensitive to IGF-I's feedback restraint (18). The present ApEn data allow the conjecture that puberty is associated with effectively reduced IGF-I negative feedback, resulting in decreased orderliness of GH release; i.e. GH secretion becomes quantifiably more irregular.

Our observations, in a pubertal context, are similar to those reported recently in another setting of withdrawn IGF-I negative feedback, namely fasting-induced decrements in plasma IGF-I concentrations (18). This open-loop (feedback-withdrawn) GH axis exhibits higher ApEn values (greater disorderliness of GH release) in men, but not women; the latter’s ApEn values are already significantly higher in the fed state than those in men (24). More generally, reduction of relevant target-tissue negative-feedback signaling in other neuroendocrine axes, such as in the gonadotropin (LH) and thyrotropic (TSH) axes via experimentally lowered serum testosterone and T4 concentrations, also brings about significant (and reversible) increases in ApEn (22, 42). Replacement of the target-organ hormones, namely T4 in the case of the TSH axis and testosterone for the LH axis, restores elevated ApEn to baseline values. Such observations in other neuroendocrine axes reinforce our interpretation that ApEn provides a useful clinical correlate of within-axis feedback integration.

Another plausible explanation for the greater disorderliness of GH release in midpuberty, and in children treated with estradiol or testosterone, is reduced coordination within the somatotropic axis, e.g. among the hypothalamus, pituitary gland, and IGF-I-synthesizing tissues. Reduced coor-
Coordination among key interacting control points within the GHRH/SRIH-GH-IGF-I axis has been inferred in acromegaly, wherein more disorderly (higher ApEn measures of) GH secretion occurs by (autonomous) GH-secreting pituitary adenomas (17). Similar inferences apply to ACTH- and aldosterone-secreting tumors (18, 20).

A third plausible interpretation of our data is that puberty and/or administration of estrogen or testosterone awakens more complex hypothalamic SRIH/GHRH interactions, as indeed are postulated to mediate the male/female gender differences in GH release in the rat and human (6, 24, 43–46). For example, in both the rodent and human, the female shows greater quantifiable irregularity of GH release than the male (24). This gender contrast is postulated to reflect inter alia decreased GH autoregulation in the female rat (47) and/or greater rhythmic hypothalamic SRIH release in the male animal (48, 49).

Changes in hypothalamic GHRH and SRIH signaling to the somatotroph population may mediate the amplification of GH secretion and the significantly higher GH ApEn values observed in midpuberty, as well as after estradiol or testosterone treatment.

And fourth, we postulate that decreased autoregulation of GHRH release could result in increased ApEn, taken as a measure of the disorderliness of GH release. This notion is supported by recent experiments in which synthetic GHRH peptide was administered iv every 90 min, as fixed pulses over 3 days, to normal men of varying ages and body compositions. Ulnaring GHRH injections consistently increased ApEn (50), thus quantifying greater irregularity of subordinate (nonpulsatile) 24-h GH release. A plausible mechanism for such increased disorderliness of the GH time series is a reduction in endogenous feedback control within the GH axis. For example, GHRH infusions may disrupt
normal physiological moment-to-moment GHRH/SRIH interactions, which otherwise reciprocally adjust each other’s release (16, 51). Merely increasing GH secretion is not relevant to increased ApEn, because ApEn is scale-invariant. Thus, a doubling of daily GH secretion rates via pyridostigmine stimulation in young men does not alter the orderliness of GH release (52). Based on the GHRH infusion data, one can speculate that a relatively intense or autonomous hypothalamic GHRH stimulus might be delivered to somatotrope cells in late puberty. This could result from either SRIH-withdrawal and/or augmented GHRH release. There are insufficient data at present to distinguish among these explanations, all of which are consistent with the (above) biostatistical considerations.

The current cross-sectional observations in boys each studied only once and stratified according to different stages of puberty (compared with young adults) do not demonstrate causality. For example, we do not know whether any given healthy boy or girl studied longitudinally throughout normal puberty would show progressively more disorderly GH release (higher ApEn) in mid-to-late puberty and then manifest a monotonic decline in ApEn in young adulthood. Sequential evaluation of the same child before and throughout puberty and again in young adulthood will be required to address this issue definitively. However, the present sex-steroid replacement studies indicate that an individual girl or boy responds to short-term estrogen or testosterone (but not DHT) treatment with increased irregularity of GH secretion akin to that identified in midpuberty. Similarly, a recent longitudinal study of prepubertal boys with idiopathic hypogonadotropic hypogonadism, treated with a very small (25 mg) dose of testosterone enanthate im, disclosed increased GH ApEn within 2 weeks (53).

Our cross-sectional data in boys and young men may not be quantitatively representative of differences expected in girls across different stages of puberty and/or in young women. Although valid in boys and men, our studies do not explain why ApEn falls postpuber tally in young adulthood after an apparent maximum in mid-late puberty, even though sex-steroid hormone concentrations remain increased. One interpretation is that the GH axis escapes mechanistically from the sex-hormone stimulus during sustained sex-hormone exposure and/or in response to adult matura tion and its metabolic consequences.

Available data also do not yet clarify whether the ApEn-implied variations in GH feedback control in puberty are singularly applicable to the somatotropic axis or also apply in the LH, FSH, ACTH, etc., feedback axes. However, an interesting parallel finding is that aging beyond the young adult years results in a slowly progressive rise in GH ApEn (19), which indicates a more disorderly GH release pattern with rising age. Diminishing regularity of neurohormone release with increasing age is also evident for LH/testosterone (25), ACTH/cortisol (20), and insulin (23). The exact mechanisms by which midpuberty and aging evoke a loss of orderliness of GH (and other hormone) release remain to be identified but likely involve alterations in the coordination and/or complexity of within-axis feedback control.

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References


ESTROGEN CONTROLS ORDERLINESS OF GH RELEASE 3419


