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Estrogens and human growth

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1. Introduction

Skeletal growth is dependent on a variety of factors, including nutrition, health status, hereditary constitution, growth factors and hormones. The summation of all these regulatory components result in a highly variable inter- and intra-individual growth rate, from conception to adulthood, with a maximum (about 8 cm per month!) at about 20 weeks of gestational age. Following this peak, there is a gradual decrease in growth rate to approximately 0.4 cm per month (5 cm per year, see Fig. 1) at age 10–12 years, just before the initiation of the so-called pubertal growth spurt. This spurt is in magnitude second only to fetal growth; it may amount to 1 cm per month or more. Eventually, growth will cease altogether after completed pubertal development. The changing hormonal milieu of the fetus, the child and the adolescent boy or girl can partly explain this highly variable growth rate, but a varying sensitivity to these regulators can also be hypothesized. Little is known about this latter area. Since the epiphyseal growth plate is the ultimate target of hormones promoting or inhibiting skeletal growth, studies on the biology of the growth plate, including hormone receptors and hormone action on epiphyseal chondrocytes, should yield important information on mechanisms of growth regulation.

Postnatal human skeletal growth can conceptually be subdivided into three components with largely different regulation: The Infantile, the Childhood and the Pubertal component (the ICP model of human growth as formulated by [1], Fig. 1). The present knowledge on the role of estrogens in these three different phases of human growth will be discussed below.

The *infancy* growth component can be regarded as a continuation of fetal growth that gradually wanes during the first 2 years after birth. Nutrition is the presently known major stimulator of fetal growth, mediated through insulin and insulin like growth factor I (IGF-I). This can be exemplified by a boy who was found to be homozygous for a null mutation of the IGF-1 gene. He was born with severe intrauterine growth retardation [2]. Likewise, the children born with the human equivalent of a 'knock-out' of the insulin receptor gene, leprechaunism, is born with severe growth retardation. Sex hormones seem to play a minor role for growth at this stage, although it has recently been shown that 46 XY girls with complete androgen insensitivity are about 2 cm shorter at birth than normal 46 XY boys, but their length is equal to that of normal girls [3]. This difference is very modest, considering the large difference in testosterone concentrations in blood of male and female fetuses [4]. Furthermore, it

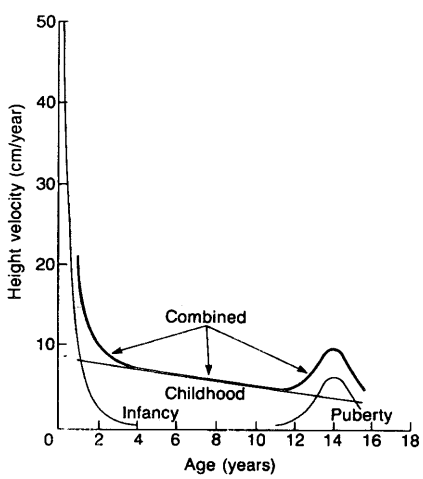

Fig. 1. The Infancy-Childhood-Puberty (ICP) model of human growth rate of boys, from birth to age 16 years. The overall (combined) growth rate is show as a bold line, while the three components are shown separately. Note the sex hormone induced rapid growth rate at early puberty, followed by cessation of growth at its completion. From Karlberg [1], with permission.

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has been shown that in untreated children with moderately severe forms of congenital adrenal hyperplasia that are exposed to elevated androgen levels in blood until diagnosis show little influence on growth before 18 months of age [5]. This suggests that the sensitivity of the human growth plate to androgenic hormones may vary, depending on age. When it comes to estrogen effects on fetal human growth, it is more difficult to draw conclusions; both male and female fetuses are exposed to very high concentrations of estradiol (1.7–17 nmol/l, reviewed by [4]). Mice with disrupted estrogen receptor α are reported to have normal birth weight, suggesting that ERα plays a minor role. The possibility remains, however, that the newly discovered ERβ might be of importance.

The regulation of the *childhood* phase of human growth is dominated by the growth hormone — IGF-1 axis. Most endocrine disorders that affect growth during this period will also effect GH and/or IGF-1. Therefore, direct effects of steroid hormones, including estrogens, on growth cartilage are difficult to distinguish from those mediated by this pathway.

A childhood disorder with elevated sex hormone concentrations in blood will manifest itself by increased growth rate, in addition to appearance of pubertal signs. Precocious puberty in both sexes is always accompanied by increased growth rate.

2. Regulation of the pubertal growth spurt

The pubertal growth spurt is primarily due to increased secretion of sex hormones (estrogens and androgens). The differential action of these hormones on growth has been amply demonstrated by studies on experiments of nature, where production of or sensitivity to androgens or estrogens is affected. Thus, it was made evident from studies of the growth pattern of 46 XY girls with androgen insensitivity syndrome (AIS, [6]) that the pubertal growth spurt is evident also in individuals with complete insensitivity to androgens. The age of maximal growth rate during puberty was found to be close to that of normal girls rather than boys (12.7 years, compared with 12.4 and 13.9 years for normal girls and boys, respectively). The magnitude of the peak height velocity (7.4 cm per year) was not different from that of normal girls (7.3 cm per year). Moreover, in one of the girls with AIS, whose testes had been removed (and thus her ability to increase testosterone production in puberty), rapid growth followed immediately upon estrogen administration that was given in order to induce female pubertal signs. Thus, it can be safely concluded that estrogens can increase growth rate even in the absence of androgen action.

It has repeatedly been demonstrated that the estrogen stimulation of growth is largely dependent on pituitary growth hormone (GH). Administration of estrogens will augment GH release in normal adolescents [18]. Furthermore, in patients with GH insensitivity (Laron's syndrome), the pubertal growth spurt has been reported to be inconspicous [7]. Thus, a major part of the stimulation of growth by estrogens is acting through the GH/IGF-1 axis. Theoretically, some of these effects might by-pass GH, either through direct action on chondrocytes or by stimulating local IGF-1 production. Since estrogen receptors have been demonstrated in growth cartilage (see below) there is a basis for a direct action of estrogens in the growth plate. The nature and mode of action of this presumed estrogen action on chondrocytes is still unknown.

Androgenic hormones such as androstendione and testosterone are obligatory precursors of estrogens through aromatization of ring A of the steroid molecule. Thus, a given dose of testosterone will have dual effects; a major androgenic action through binding to the androgen receptor (with or without prior metabolism to dihydrotestosterone), and to a minor extent through the estrogen receptors, after aromatisation to estrogens. An androgenic hormone that cannot be aromatized (dihydrotestosterone [DHT], oxandrolone, a.o) will thus work as a 'pure' androgen. It has been shown that DHT [8] or oxandrolone [9] given to boys with delayed puberty will accelerate growth rate, but do not change the blood levels of GH or IGF-1. Androgen receptors have been demonstrated in chondrocytes in growth plates (Abu et al., 1997), thus making direct effects of androgens on chondrocytes possible but not proven.

3. Dual effects of estrogens on growth

Apart from stimulating growth, estrogens also seem to be responsible for the ossification of the growth plate that finally causes cessation of growth in late puberty. This has been amply shown by two rare disorders; One man with homozygous disruptive mutations in the estrogen receptor α (ERα, [10]) and two patients with inability to synthesize estrogens due to a defect in the aromatase gene [11,12]. In both the cases, the growth plates failed to ossify fully, in spite of normal masculinization of skin (sexual hair, acne, apocrine sweat glands) and genitalia. Consequently, growth still continues at the latest report (at age 28 years) on the estrogen insensitive man, and for the men with aromatase deficiency it was not stopped until estrogen medication was started [13]. Osteoporosis was a main complaint in both the diseases, proving that estrogens are needed to achieve normal bones also in males.

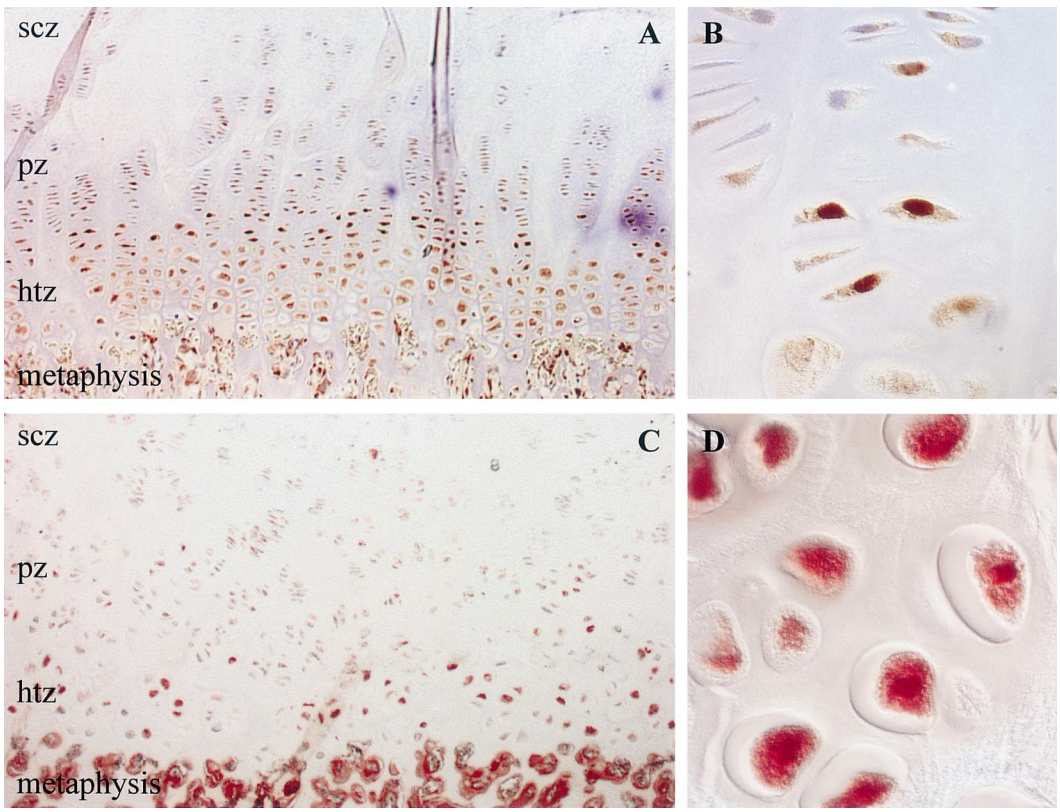

Fig. 2. Immunohistochemical staining of estrogen receptor-α (A, B) and -β (C, D) in proximal tibial growth plates from a boy at early puberty. (A) Estrogen receptor-α (ERα) immunoreactivity was detected in stem, proliferative and hypertrophic zones of the growth plate. (B) High power magnification of the transition from proliferative to hypertrophic zone with mainly nuclear staining of ERα positive cells. (C) Cells immunopositive to estrogen receptor-β (ERβ) are mainly detected in the hypertrophic zone. (D) High power magnification of the hypertrophic zone revealed intense staining of ERβ in the chondrocytes. scz, stem cell zone, pz, proliferative zone, htz, hypertrophic zone.

The capacity of estrogens to enhance the rate of closure of the growth plates has been known and used in clinical endocrinology since long: large doses of estrogens given to girls with expected 'excessive' tall stature has been shown to limit further growth, compared to controls [14]. At least under certain conditions, this seems to be true also for lower estrogen doses. Administration of estrogens to girls with Turner's syndrome that were already on treatment with GH caused an earlier cessation of growth and lower final height than that found for a parallel group that was given estrogens at a later age [15].

4. Estrogen receptors in growth cartilage

ERα has previously been shown to be expressed in all layers of the human growth plate [16]. This finding, as well as the uninhibited growth of the man with ERα gene disruption [10] suggests that ERα is involved in apoptosis of chondrocytes and the subsequent ossification. We recently demonstrated the presence of immunoreactivity for ERβ in the hypertrophic chondrocytes of human growth plates (Fig. 2, [17]). The functions of these receptors remain to be determined — evidently, they could not fully substitute for the ERα in the ERα-deficient man, who is reported to have intact ERβ mRNA (Korach, personal communication, 1999).

Contrary to the situation in man, the legs (femur) of the female ERα knock-out mouse (alphaERKO mouse) is shorter than what is found in normal littermates, while the length of the spine is normal [19]. Possibly, this is explained by the lower than normal levels of IGF-1 (76%) noticed in the alphaERKO mouse.

5. Conclusions

In conclusion, estrogens have a dual action on human growth; they *stimulate* growth though increasing the secretion of growth hormone (GH) from the pituitary, and possibly through direct effects on the growth plates. They also *inhibit* growth at the end of puberty in both sexes by causing ossification of the growth plate. The mechanisms of action of estrogens directly on the growth cartilage and the functions of ERα and ERβ in this respect remain to be determined.

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References

[1] J. Karlberg, On the construction of the infancy-childhood-puberty growth standard, Acta Paediatr. Scand. (Suppl.) 356 (1989) 26–37.

[2] C. Camacho-Hubner, K.A. Woods, F. Miraki-Moud, P.C. Hindmarsh, A.J. Clark, Y. Hansson, A. Johnston, R.C. Baxter, M.O. Savage, Effects of recombinant human insulin-like growth factor I (IGF-I) therapy on the growth hormone-IGF system of a patient with a partial IGF-I gene deletion, J. Clin. Endocrinol. Metab. 84 (5) (1999) 1611–1616.

[3] F. de Zegher, I. Francois, A.L. Boehmer, G. Saggese, J. Muller, O. Hiort, C. Sultan, P. Clayton, R. Brauner, E. Cacciari, L. Ibanez, G. Van Vliet, A. Tiulpakov, N. Saka, M. Ritzen, W.G. Sippell, Androgens and fetal growth, Horm. Res. 50 (4) (1998) 243–244.

[4] J.R. Pasqualini, F.A. Kincl, Hormones and the Fetus, Pergamon Press, Oxford, 1984, p. 226.

[5] A. Thilén, K.A. Woods, L.A. Perry, M.O. Savage, A. Wedell, E.M. Ritzén, Early growth is not increased in untreated moderately severe 21-hydroxylase deficiency, Acta Paediatr. 84 (1995) 894–898.

[6] M. Zachmann, A. Prader, E.H. Sobel, J.F. Crigler, E.M. Ritzén, M. Atarés, A. Ferrandez, Pubertal growth in patients with androgen insensitivity, Indirect evidence for the importance of estrogens in pubertal growth of girls, J. Pediatr. 108 (1986) 694–697.

[7] Z. Laron, A. Pertzelan, Puberty in Laron-type dwarfism — a model for untreated congenital isolated growth hormone deficiency, in: H. Frisch, Z. Laron (Eds.), Induction of Puberty in Hyppituitarism. Review: Serono Symposia, vol. 16, 1988, pp. 39–48.

[8] G.D. Eakman, J.S. Dallas, S.W. Ponder, B.S. Keenan, The effects of testosterone and dihydrotestosterone on hypothalamic regulation of growth hormone secretion, J. Clin. Endocrinol. Metab. 81 (3) (1996) 1217–1223.

[9] A. Malhotra, E. Poon, W.Y. Tse, P.J. Pringle, P.C. Hindmarsh, C.G. Brook, The effects of oxandrolone on the growth hormone and gonadal axes in boys with constitutional delay of growth and puberty, Clin. Endocrinol. (Oxford) 38 (4) (1993) 393–398.

[10] E.P. Smith, J. Boyd, G.R. Frank, H. Takahashi, R.M. Cohen, B. Specker, T.C. Williams, D.B. Lubahn, K.S. Korach, Estrogen resistance caused by a mutation in the estrogen receptor gene in a man, New Engl. J. Med. 331 (1994) 1056–1061.

[11] A. Morishima, M.M. Grumbach, E.R. Simpson, C. Fisher, K.J. Qin, Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens, Clin. Endocrinol. Metab. 80 (12) (1995) 3689–3698.

[12] C. Carani, K. Qin, M. Simoni, M. Faustini-Fustini, S. Serpente, J. Boyd, K.S. Korach, E.R. Simpson, Effect of testosterone and estradiol in a man with aromatase deficiency, New Engl. J. Med. 337 (2) (1997) 91–95.

[13] J.P. Bilezikian, A. Morishima, M.M. J. Bell, Grumbach, Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency, New Engl. J. Med. 339 (9) (1998) 599–603.

[14] H. Svan, E.M. Ritzén, K. Hall, L. Johansson, Estrogen treatment of tall girls: dose dependency of effects on subsequent growth and IGF-I levels in blood, Acta Paediatr. Scand. 80 (1991) 328–332.

[15] K.O. Nilsson, K. Albertsson-Wikland, J. Alm, S. Aronson, J. Gustafsson, L. Hagenäs, A. Häger, S.A. Ivarsson, J. Karlberg, B. Kriström, C. Marcus, C. Moell, M. Ritzén, T. Tuvemo, C. Wattsgård, U. Westgren, O. Westphal, J. Åman, Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone, J. Clin. Endocrinol. Metab. 81 (1996) 635–640.

[16] V. Kusec, A.S. Virdi, R. Prince, J.T. Triffitt, Localization of estrogen receptor-alpha in human and rabbit skeletal tissues, J. Clin. Endocrinol. Metab. 83 (7) (1998) 2421–2428.

[17] L.O. Nilsson, A. Boman, L. Savendahl, G. Grigelioniene, C. Ohlsson, E.M. Ritzen, J. Wroblewski, Demonstration of estrogen receptor-beta immunoreactivity in human growth plate cartilage, J. Clin. Endocrinol. Metab. 84 (1) (1999) 370–373.

[18] G. Marin, H.M. Domene, K.M. Barnes, B.J. Blackwell, F.G. Cassorla, G.B. Cutler, The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys, J. Clin. Endocrinol. Metab. 79 (2) (1994) 537–541.

[19] O. Vidal, M. Lindberg, L. Sävendahl, D.B. Lubahn, E.M. Ritzen, J.A. Gustafsson, C. Ohlsson, Disproportional body growth in female estrogen receptor-alpha-inactivated mice, Biochem. Biophys. Res. Commun. 265 (2) (1999) 569–571.