Molecular and Cellular Endocrinology 254–255 (2006) 207–216

Molecular and Cellular Endocrinology

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Use of aromatase inhibitors to increase final height

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Abstract

During puberty in both sexes, the mechanism involved in epiphyseal fusion is mediated by the action of estrogen through a cascade of events including proliferation, differentiation, and apoptosis of chondrocytes. The enzyme P450 aromatase catalyzes the aromatization of C_{19} androgens (androstenedione and testosterone) to C_{18} estrogens (estrone and estradiol). Inhibition of estrogen action by aromatase inhibitors (AIs) appears to decelerate the process of growth plate fusion, and thus AIs may be used therapeutically to increase adult height. The clinical experience with AIs in the pediatric setting is limited to testolactone, fadrozole, letrozole, and anastrozole. Testolactone, a nonselective steroidal AI, has been used successfully as an adjunct to antiandrogen and gonadotropin-releasing hormone analogue (GnRHa), therapy for children with familial male-limited precocious puberty (FMPP) and congenital adrenal hyperplasia (CAH), and with some success in girls with McCune–Albright syndrome. The limitations of testolactone include its relatively low potency and the need for frequent dosing. Results of a randomized placebo-controlled trial in boys with delayed puberty treated with letrozole, a selective nonsteroidal AI, found that boys treated with letrozole + testosterone experienced delayed bone maturation and good growth response and achieved an increase in predicted adult height. In this study, only minor differences in bone density were seen between the placebo and letrozole treatment groups, both of which were receiving concomitant testosterone therapy. No adverse effects on testis size or inhibin B concentration were noted. The therapeutic value of AIs in growth promotion now remains to be substantiated in future controlled clinical trials.

Keywords: Height growth; Bone age; Growth plate; Short stature; Stature; Aromatase inhibitor; Chondrocyte; Estrogen

1. Estrogen and growth

In 1994, the case report of a man with inactivating mutation of the estrogen receptor (ER) revolutionized the traditional concept of the roles of sex steroids in males (Smith et al., 1994). This 28-year-old man was 204 cm tall, yet he had a bone age of 15 years with open epiphyses of long bones, and consequently he was still growing. Moreover, he had no recollection of accelerated pubertal growth despite otherwise normal pubertal development. Soon thereafter, two males with similar phenotypes were described (Morishima et al., 1995; Carani et al., 1997). In these men, the effects of estrogens were suppressed due to mutations in the gene coding for P450 aromatase enzyme, which converts androgens to estrogens. Administration of estrogen led to closure of the epiphyses and discontinued growth (Carani et al., 1997; Bilezikian et al., 1998). In all of these men, concentrations of androgens were normal or above normal. These case reports confirmed that estrogens are essential hormones for epiphyseal closure in males. Moreover, the reports suggest that estrogens probably do not participate in the regulation of linear growth, but they induce growth acceleration during puberty. This newly discovered specific role of estrogen in growth regulation has significantly increased scientific interest in the use of specific AIs in treatment of patients with short stature.

In premenopausal women, the source of estrogens is predominantly ovarian in origin. After menopause, estrogens are mainly synthesized in peripheral tissues (e.g., adipose tissue, skin, muscle, breast tissue, and bone) through local aromatization of circulating androgens, which are mostly produced by the adrenals, to estrogens (Labrie et al., 1997). P450 aromatase is the enzyme that catalyzes the aromatization of C_{19} androgens (androstenedione and testosterone) into C_{18} estrogens (estrone and estradiol) (Fig. 1). In males, it has been estimated that, at best, the aromatase from testes accounts for about 15% of circulating estrogens; hence, extragonadal production of estrogens is as physiologically important to men as to postmenopausal women (Labrie et al., 1997). The same is probably also true for prepubertal children. Therefore, the circulating levels of testosterone produced by the testes in males must be efficiently converted by the P450 aromatase at extragonadal sites to give rise to local concentrations of estradiol sufficient to locally transactivate the ER in estrogen-dependent tissues.

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doi:10.1016/j.mce.2006.04.031

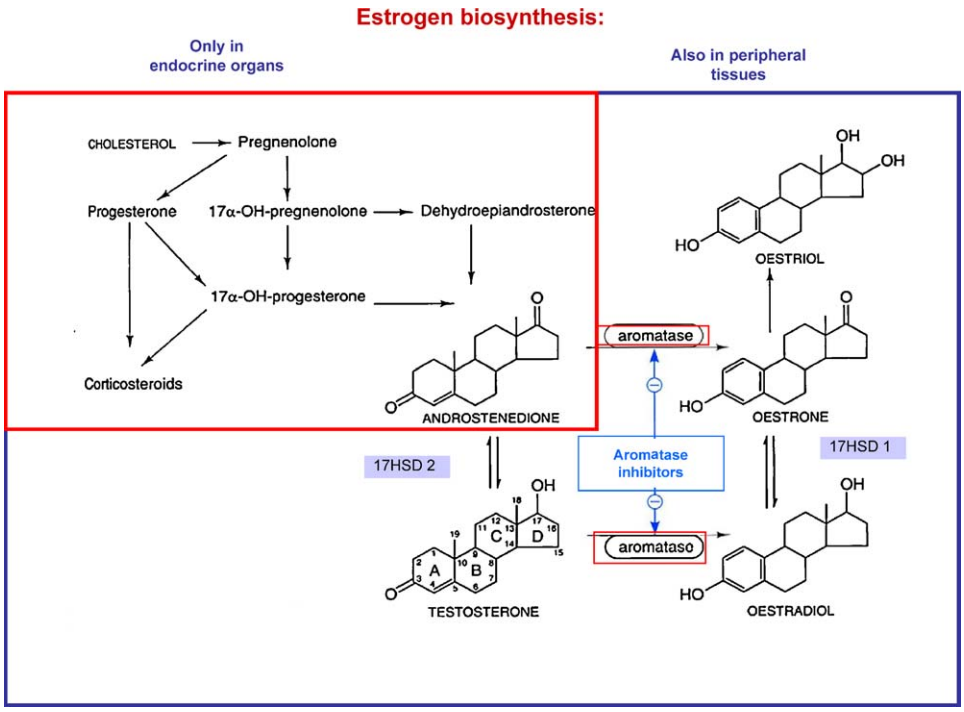

Fig. 1. P450 aromatase catalyzes the aromatization of C_{19} androgens (androstenedione and testosterone) to C_{18} estrogens (estrone and estradiol). 17β-HSD = 17β-hydroxysteroid dehydrogenase.

Estrogen biosynthesis at these extragonadal sites possesses certain fundamental features that differ from ovarian estogen biosynthesis. For instance, extragonadal estrogen biosynthesis is dependent on circulating precursor C_{19} steroids, and the estrogen synthesized within these compartments, particularly in the bone, breast, and brain, is probably biologically active only at the level of local tissue in a "paracrine" or "intracrine" fashion (Fig. 1) (Labrie et al., 1997; Grumbach and Auchus, 1999).

2. AIs

Several pharmaceutical compounds have been developed to inhibit activity of P450 aromatase (Santen, 2003). In the 1960s, clinical trials with the first-generation AI, aminoglutethimide, provided practical proof that AIs could be used for treatment of hormone-dependent breast cancer (Santen et al., 1990). However, aminoglutethimide had substantial side effects, which diminished its usefulness. Over the last 30 years, several more potent and selective but less toxic AIs have been developed (Sainsbury, 2004; Miller, 2004). These new inhibitors can be divided into two categories with respect to their mechanisms of action: (1) *Steroidal inactivators*, which bind covalently to the active site of the enzyme and irreversibly destroy its enzymatic action. These compounds are also called suicide or mechanism-based inactivators and (2) *Nonsteroidal competitive inhibitors*, which bind to the active site of the aromatase enzyme and block estrogen formation. The current, third-generation compounds are nearly completely selective for the P450 aromatase enzyme, are between 1000- and 10,000-fold more potent than aminoglutethimide, and are much better tolerated. In several countries some of these third-generation AIs have been approved for clinical use in hormone-dependent breast cancer. The chemical structures of four competitive nonsteroidal AIs (aminoglutetimide, anastrozole, fadrozole, and letrozole) and two steroidal AIs (formestane and exemestane) are shown in Fig. 2.

3. Use of AIs in children

Estrogen appears to be important for normal bone growth and mineralization not only of human females, but also of human males (Oz et al., 2000; Sasano et al., 1997). Analyses conducted using immunohistochemistry and in situ hybridation techniques suggest that aromatase is widely expressed in bone tissue of men and women, supporting previous findings that bone in both men and women has the capacity to convert androgen to estrogen in the bone (Sasano et al., 1997). These data, together with data obtained from the clinical cases of inactivating mutations in ERα and P450 aromatase genes (Smith et al., 1994; Morishima et al., 1995; Carani et al., 1997), provide the rationale for using AIs to promote longitudinal growth. To date, four AI compounds have been used in children to promote growth: testolactone (Laue et al., 1989, 1993; Leschek et al., 1999; Merke et al., 2000; Feuillan et al., 1986, 1993), anastrozole (Mauras et al., 2000; Roth et al., 2002; Kunz et al., 2003), fadrozole (Nunez et al., 2003), and letrozole (Wickman et al., 2001, 2002; Wickman and Dunkel, 2001; Feuillan et al., 2003) (Table 1). The same doses of AIs prescribed to adults have been used in children, likely because the adverse effects reported in older patients are generally mild to moderate.