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Effects of estradiol-17β, testosterone and a black cohosh preparation on bone and prostate in orchidectomized rats

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Abstract

Estradiol (E_2) and testosterone (T) effectively prevent orchidectomy (orx) induced osteoporosis. T, however, stimulates prostate proliferation which may lead to malignancy. We showed that a *Cimicifuga racemosa* (CR) preparation had bone-sparing effects without exerting estrogenic effects in the uterus. We studied therefore whether a CR preparation has also antiosteoporotic effects in orx rats substituted with E_2, T or CR via pelleted food over a period of 3 months. Average daily intake per animal was: T: 25 mg; E_2: 0.325 mg, CR low dose: 33 mg; CR high dose: 133 mg. E_2, T and CR at the high dose partially prevented development of osteoporosis as measured by quantitative computer tomography in the metaphysis of the tibia. E_2, but not T or CR reduced serum osteocalcin and the metabolic products of collagen-1α1. Gene expression of collagen-1α1 and tartrate-resistant acid phosphatase was decreased by E_2 and the higher dose of the CR extract but increased in the T-treated animals. In the prostate T inhibited androgen receptor, estrogen receptor α and insulin-like growth factor-1 gene expression but stimulated the expression of the ERβ gene. These effects were not shared by E_2 or both doses of the CR extract. It is concluded that E_2, T and CR exert antiosteoporotic effects in the metaphysis of the tibia of orx rats. T has profound effects in the prostate which were not seen in the E_2- and CR-treated animals. Therefore, the *Cimicifuga racemosa* extract BNO 1055 may be useful to prevent osteoporosis in aged male patients with reduced testosterone production.
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1. Introduction

The castrated rat is an excellent model to study development and effects of treatment of osteoporosis [1]. In female rats it is well established that estradiol (E_2) replacement will largely prevent development of osteoporosis [2]. In male orchidectomized (orx) rats the matter is more complicated because not only testosterone (T) but also E_2 are effective to maintain bone mineral density (BMD) [3]. The role of E_2 seems to be physiologic as the bones of males express aromatase and estrogen receptors (ER) [4–6]. Furthermore, male ERα *knock-out* mice develop severe defects, primarily of trabecular structures of long bones. Normal bone

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homeostasis in gonad-intact rats is maintained by an equilibrated activity of osteoclasts and osteoblasts. Due to the activity of multinucleated osteoclasts lacunae are digested in the cancellous bone and this activity is signal for osteoblasts which initiate the appropriate repair mechanisms. Following orx, the activity of these two cell types is increased, the activity of osteoclasts more than that of osteoblasts [7]. Hence, bone resorption exceeds bone formation at a high metabolic level. The activity of osteoclasts can be monitored by quantifying the mRNA concentrations for tartrate-resistant acid phosphatase (TRAP) [8]. In the serum increased bone resorption reflects in increased levels of the metabolic product of the bone-specific collagen-1α1 (Coll1), the C-terminal telopeptides of type I collagen (CTx) [9]. Osteoblast activity can be monitored by determining the expression of a variety of genes or their proteins: insulin-like growth factor 1 (IGF1), osteocalcin (OC), and Coll1 are all products of osteoblasts and their mRNA concentrations indicate the degree of osteoblastic activity in forming new bone (IGF1, osteocalcin, Coll1) [2,10]. In the serum osteocalcin and the metabolic products of Coll1, i.e. the CTx, can be measured as an additional surrogate parameter of osteoblast or osteoclast activity [2]. The availability of quantitative computer tomography (qCT) [11] for the determination of bone mineral density (BMD) of trabecular and cortical bone structures in a variety of bones plus the availability of sensitive markers of bone metabolism in the serum allows studies of development and effects of treatments of an osteoporosis in experimental animals like male rats.

While it is known that testosterone and estrogens have beneficial effects in the bone, it is less clear whether testosterone alone or together with estradiol causes proliferation of prostate tissue and whether this may eventually facilitate development of prostate cancer [12,13]. In searching for a second androgen receptor Gustafsson and his colleagues succeeded to clone the second estrogen receptor which is the ERβ [14]. This receptor is amply expressed in prostate epithelial cells [15,16] and ERβ knock-out mice develop hyperplastic prostates [17]. Hence, endogenous estradiol-17β or other locally formed ERβ ligands may play an important role in the function of the prostate. The fact that androgens plus estrogens may have undesired effects such as in the prostate has led to intensive research for selective androgen receptor modulators (SARMs) with desired effects in the bone and with no effect in the prostate. Similarly, selective estrogen receptor modulators (SERMs) may be useful to prevent osteoporosis in hypogonadal individuals, i.e. in orx rats and in aged male humans. Indeed, raloxifene, a SERM with osteoprotective effects in the female bone, was shown to also protect the bones of orx rats from osteoporosis [18].

Recently, phytoestrogens came into the focus of bone research because there is increasing evidence that they might have osteoprotective effects [19]. Black cohosh (*Cimicifuga racemosa* = (CR)) was shown to have antiosteoporotic effects in ovariectomized rats [2,20] and there is circumstantial evidence that it may have similar effects in the bone of postmenopausal women [21]. The CR extract also reduced LH levels in rats and climacteric complaints in postmenopausal women but had no effects in the uteri of ovx rats or on the endometrium of postmenopausal women [21,22]. Therefore, compounds in the CR extracts were suggested to exert organ selective estrogen-like i.e. selective estrogen receptor modulator (SERM) activity [21,22]. We have been showing earlier that CR does not bind to both known subtypes of ERs which rises the possibility that other than ER-mediated mechanisms are involved in the osteoprotective effects of CR [21,22]. Aged men develop also an osteoporosis, though to a lesser degree than females. Nevertheless, approximately 10% of males aged over 70 develop osteopenia and later osteoporosis. Treatment of aged men with estrogens has severe side effects, such as development of mammary gland tissue, and testosterone treatment increases the risk to develop a prostate cancer. Therefore, substances of plant origin without unwanted estrogenic effects and without increasing the risk for the prostate would be highly desirable. Therefore, in the present study we compared the effects of a chronic (3 months) E_2/T treatment with those of the CR extract BNO 1055 in the bone and in the prostate.

We measured BMD of the proximal metaphysis of the tibia and of the cortical structures of the tibia in orx male rats which were treated for 3 months with E_2, T or 2 doses of the CR extract BNO 1055. In addition, we measured serum osteocalcin as a marker of osteoblast activity as well as the metabolic product of collagen-1α1, the CTx, and compared the effects of an E_2 or T treatment with those of a 3-months treatment with 2 doses of the CR extract BNO 1055. If this CR extract would prove to be beneficial on osteoporosis also in

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