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The antagonist properties of Bazedoxifene after acute treatment are shifted to stimulatory action after chronic exposure in the liver but not in the uterus

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ABSTRACT

A promising alternative to conventional hormone therapy for postmenopausal symptoms is treatment combining Bazedoxifene (BZA), a third-generation selective estrogen receptor modulator (SERM), and conjugated equine estrogen (CE). This combination is also known as a tissue-selective estrogen complex (TSEC). Understanding the tissue-specific actions of SERMs and the TSEC remains a major challenge to try to predict their clinical effects.

The aim of this study was to compare acute *versus* chronic treatment with BZA, CE or CE + BZA in two major targets of estrogens, the uterus and the liver. In these two tissues, acute treatment with CE, but not with BZA, induced similar gene expression change than the most important endogenous estrogen, 17-β estradiol (E2). Acute induction of gene expression by E2 or by CE was antagonized by the addition of BZA. Concomitantly, BZA alone or in combination with E2 or CE induced a partial degradation of ERα protein after acute exposure. In uterus, chronic treatment of BZA alone had no impact on tissue weight gain or on epithelial cell proliferation, and also antagonized CE-effect in uterus, thereby mimicking the acute effect. By contrast, in the liver, chronic BZA and CE + BZA elicited agonistic transcriptional effects similar to those of CE alone. In addition, at variance to BZA acute effect, no change in ERα protein abundance was observed after chronic treatment in this tissue.

These experimental *in vivo* data highlight a new aspect of the time-dependent tissue–specific action of BZA or TSEC, *i.e.* they can act acutely as antagonists but become agonists after chronic treatment. This shift was observed in liver tissue, but not in proliferative sex target such as the uterus.

1. Introduction

The decline of estrogen levels after menopause is associated with bone loss, hot flushes and vulvar–vaginal atrophy, affecting sexual function, relationships, and quality of life. Estrogen–progestin therapy was previously considered as the standard for managing moderate to severely bothersome symptoms associated with menopause but this drug combination is now controversial due to the increased risk of breast cancer and thromboembolism (Anderson et al., 2004; Chlebowski et al., 2003; Rossouw et al., 2002). The combination of conjugated estrogen (CE) with Bazedoxifene (BZA) is known as the tissue-selective estrogen complex (TSEC). It was designed to minimize the undesirable effects of hormone therapy on breast tissue yet allow the beneficial effects of estrogen on other estrogen-target tissues, thus suppressing climacteric symptoms and preventing osteoporosis (Mirkin and Komm, 2013). This drug combination was developed by Pfizer and has been marketed in the US for 2 years as Duavee® (CE, 0.45 mg/BZA, 20 mg). It has also been approved by the

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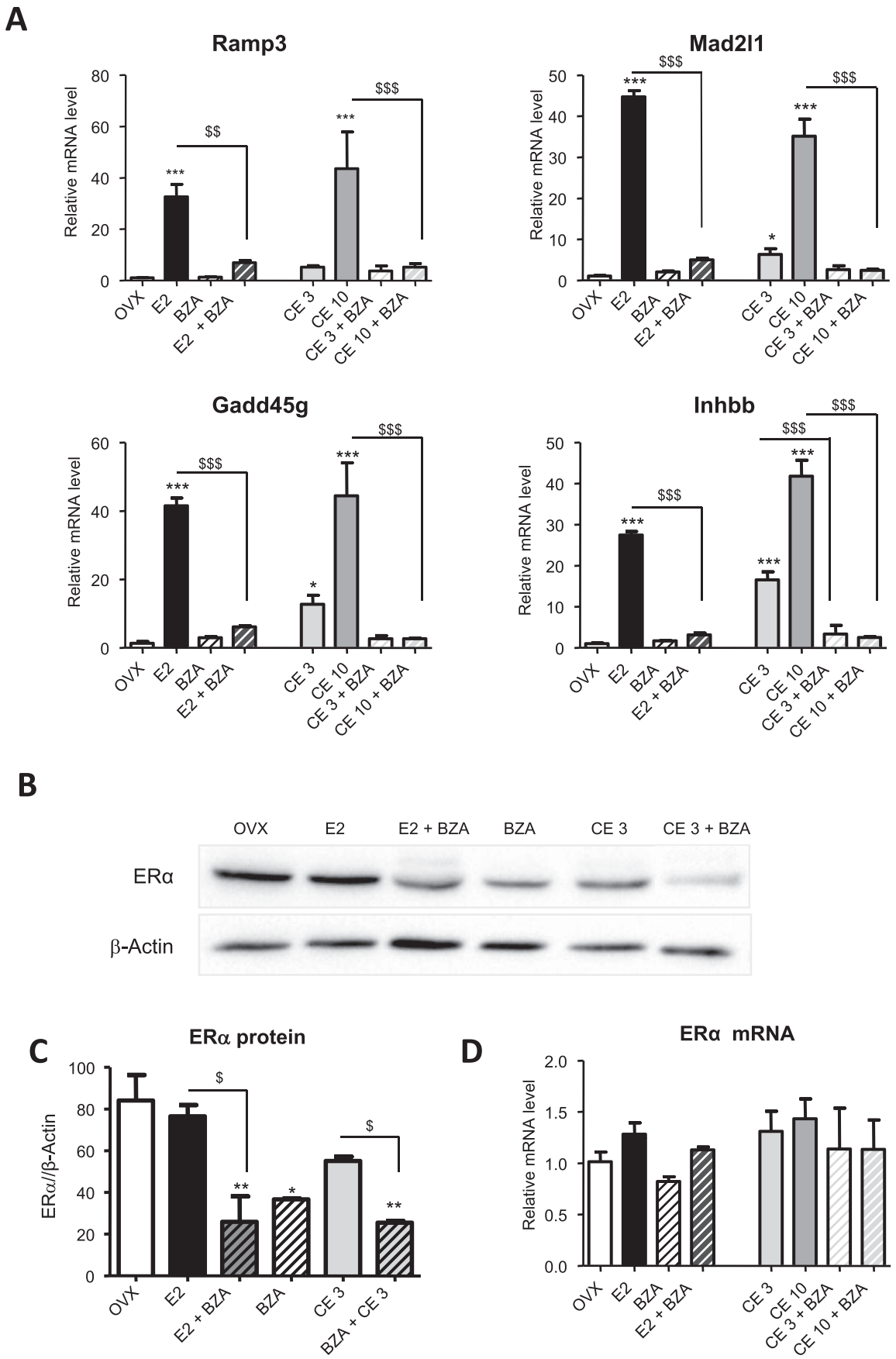

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