



Differential effect of the 17 β -aminoestrogens prolame, butolame and pentolame in anxiety and depression models in rats

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ABSTRACT

Estrogens of clinical use produce consistent antidepressant- and anxiolytic-like effects in animal models of menopause. Regulation of the hypothalamic–pituitary–adrenal (HPA) or stress axis, has been proposed as a pathway through which estrogens improve affective-like behaviors. Anticoagulant 17 β -aminoestrogens (17 β -AEs) butolame and pentolame mimic some effects of estradiol (E₂), i.e., on female rodent sexual behavior, with opposite actions on coagulation. However, their psychoactive actions have not been explored. On the basis of similitude with E₂'s effects, we hypothesized that these 17 β -AEs would induce anxiolytic- and antidepressant-like effects, which would be reflected in a reduction of activity in the HPA axis. In ovariectomized female rats, chronic treatment with prolame (60 μ g/kg), butolame (65 μ g/kg) and pentolame (70 μ g/kg) reduced anxiety-like behavior in the elevated plus maze (evidenced by an increase in time in open arms, E₂ (40 μ g/kg) + 176%; prolame + 201%; butolame, + 237%; and pentolame + 295%, in comparison to the control vehicle group 100%). Pentolame also decreased significantly anxiety-like behavior in the burying behavior test. Prolame and E₂ produced a significantly antidepressant-like action, which was not induced by butolame and pentolame. Behavioral effects of 17 β -AEs (and E₂) on anxiety and depression did not follow the same pattern than corticosterone or E₂ levels; they also were associated to changes in locomotor activity, evaluated by the open field test. These results constitute the first evidence of specific and selective actions of butolame and pentolame as anxiolytics for females with a hypoestrogenic condition. Results also confirm the potential of prolame as an antidepressant steroid with equivalent actions to E₂. Psychoactive properties of 17 β -AEs in combinations with reduced adverse effects on coagulation, suggest that 17 β -AEs may be a good alternative replacement therapy for women with symptoms associated with menopause.

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1. Introduction

Recent studies investigating affective processes in humans have observed higher rates of mood and anxiety disorders in pathologies related with abnormalities in gonadal hormone levels (Rasgon et al., 2002). In women during menopause transition, diminishing ovarian function gradually leads to decreases of 17 β -estradiol (E₂) levels. Such status is linked to physical (i.e., hot flushes) and psychological (i.e., changes in mood) symptoms (Llaneza et al., 2012). Extreme manifestations of anxiety and sadness in women with risk factors, may lead to the

diagnosis of anxiety and depressive disorders impacting their quality of life (Terauchi et al., 2013).

Traditional psychiatric drugs may improve affective alterations of menopausal women (Morgan et al., 2005); however, the complex symptoms due to the lack of gonadal hormones sometimes require the use of estrogen replacement therapy (ERT). ERT has benefits on metabolism, hot flushes and insomnia (Llaneza et al., 2012), improves mood alterations and reduces anxiety in some women (Rasgon et al., 2002; Soares et al., 2001). Importantly, ERT may modulate hypothalamic–pituitary–adrenal (HPA) axis function (Kudielka et al., 1999; Pattacchioli et al., 2006) exerting its antidepressant and anxiolytic effects in women. However, adverse effects of ERT such as an increased risk of breast or endometrial cancer and thromboembolic events (Farquhar et al., 2009; Narod, 2011), limits its use in high risk populations for these diseases.

Rodent models have been extensively used and have made an important contribution on better understanding ERT's effects on

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anxiety- or depressive-like behaviors and its underlying mechanisms (Estrada-Camarena et al., 2010; Walf and Frye, 2005a). Estrogen actions on affective-like behavior are influenced by many factors. Estrogens like E_2 and ethynilestradiol produce consistent antidepressant-like effects in hypoestrogenic female rodents, with some variation in efficacy related to dosage (Estrada-Camarena et al., 2003; Walf and Frye, 2005a). Their effects on anxiety are more controversial even in animal models. Conflicting results seem be linked to the type of estrogen evaluated, but more importantly to the regimen (Hiroi et al., 2011; Kalandakanond-Thongsong et al., 2012). Considering the advantages of ERTs, there continues to be interest in finding new estrogenic molecules with an adequate balance between benefits and risks. Effects of these molecules on affective regulation are investigated from a basic approach in validated animal models of anxiety- or depressive-like behaviors.

The synthetic 17 β -aminoestrogens (17 β -AEs), prolame [17 β -(3-hydroxy-1-propylamino)-1,3,5(10)-(estratrien-3-ol)], butolame [17 β -(3-hydroxy-1-butylamino)-1,3,5(10)-estratrien-3-ol], and pentolame [17 β -(5-hydroxy-1-pentylamino)-1,3,5(10)-(estratrien-3-ol)] are E_2 analogs with an amino-alcohol side chain $-NH-(CH_2)_n-OH$ substituent in the C17 position of the steroid nucleus (Fig. 1). 17 β -AEs in ovariectomized (Ovx) rodents produce effects on uterus, brain, and stimulate sexual behavior similarly to E_2 , but with lower efficacy and potency (Jaimez et al., 2000; Lemini and Cancchola, 2009; Lemini et al., 2005b). Interestingly, 17 β -AEs induce anticoagulant effects, in contrast to the procoagulant effect of E_2 (Lemini et al., 2005a), which may have implications for their use as ERT in women with increased risk of thromboembolic events.

Recent studies in behavioral paradigms have reported that prolame has psychoactive actions, similar to E_2 . Prolame induces mnemonic, anxiolytic-like (Limón et al., 2012), and antidepressant-like effects in OvX females (Lemini et al., 2013). Butolame and pentolame have a close structural relationship to prolame, but differences in the length of chain substituent (Jaimez et al., 2000) account for less adverse effects on coagulation and in the uterus (Lemini et al., 2005a,b). However their psychoactive effects have been scarcely investigated in animal models of affective disorders.

This study tested the hypothesis that treatment with butolame and pentolame would produce antidepressant- and anxiolytic-like effects similar to the natural hormone (E_2). We predicted that these effects would be associated to a chronic administration regimen rather than a subacute one (Koss et al., 2004; Lemini et al., 2013). Considering the psychoactive effects of E_2 could be related to an adequate stress response, it was expected that 17 β -AEs' actions on behavior were associated with reduction of corticosterone (B) levels in blood. Accordingly, the objectives of this study were: a) to evaluate whether chronic administration of butolame or pentolame produce anxiolytic- and/or antidepressant-like effects in validated animal models of affective disorders; b) to determine possible unspecific effects of steroids on ambulation by using the open field test (OFT); c) to relate behavioral effects of 17 β -AEs with serum levels of B; and d) to investigate if behavioral effects of 17 β -AEs were linked to production of E_2 levels.

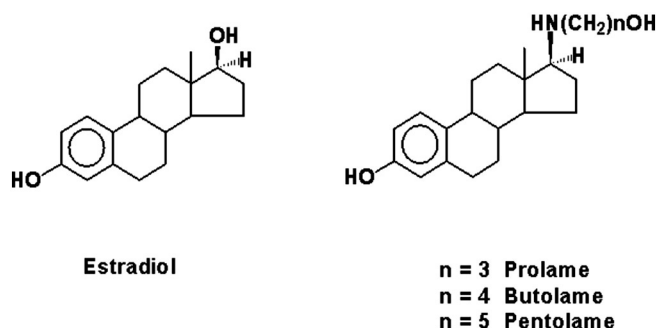


Fig. 1. Structure of 17 β -estradiol and 17 β -AEs.

2. Methods

2.1. Animals

Female adult Wistar rats weighing 200–250 g were used in this study. All animals were bred in the animal housing facilities of the Faculty of Medicine, UNAM; treated and evaluated in the National Institute of Psychiatry “Ramón de la Fuente Muñiz”. The animals were housed, five per cage, in a room under inverted light/dark cycle conditions (12/12 h; lights on at 22:00 h) with ad libitum access to water and Purina Rat Chow throughout the experiments. Institutional ethical committees for animal use approved the protocol for these experiments (No. 058-2014 and No. NC143370.1). Animal management was done according to the general principles of laboratory animal care (NIH publication 85-23, 1985, cited in National Research Council, 2011). Experimental studies were conducted in accordance with Norma Oficial Mexicana NOM-062-ZOO-1999, the Animal Protection Law for the Federal District and the General Health Law Related to Health Research (2001).

2.2. Surgery

Rats were bilaterally OvX under anesthesia with 2,2,2-tribromoethanol (Fluka, 100 mg/kg i.p., dissolved in 0.9% saline solution) and kept in aseptic conditions. Afterwards, the rats were returned to their home cages to allow recovery for three weeks, before treatment administration (Lemini et al., 2013).

2.3. Drugs

Prolame, butolame and pentolame were synthesized from estrone. The detailed process for the synthesis of these 17 β -AEs is described elsewhere (Fernandez-G et al., 1985). Substances were subjected to proof of chemical purity by comparing their analytical (MP, TLC) and spectroscopic methods (IR, NMR, MS) with the authentic samples. E_2 (3,17 β -dihydroxy-1,3,5(10)-estratriene) was purchased in Sigma-Aldrich (St. Louis MO, USA). All steroids were dissolved in corn oil.

2.4. Behavioral tests

2.4.1. Elevated plus maze test (EPM)

This test based on exploration was conducted under red dim light. Animals were exposed to a non-painted wood, plus-shaped maze, made with four arms (50 × 10 cm) placed on an elevated platform (50 cm from the floor). Opposite arms were surrounded by walls (40 cm high), while the others were kept without protection. Rats were placed in the center of the maze facing an open arm and left to explore during 10 min, under red illumination. Sessions were videotaped and behavior analyzed later by two independent observers to quantify the following variables: time (seconds) spent exploring the center, open or closed arms, and the total number of crossing from the open to closed arms (or vice-versa). A rat is considered to cross to an arm when it puts its four paws in that place. An increased time in the open arms was interpreted as an anxiolytic-like effect, while changes in total number of crossing were considered to reflect variations in locomotor activity (Fernández-Guasti et al., 1999).

2.4.2. Burying behavior test (BBT)

All procedures were conducted under red dim light. Three days before the test, rats were habituated to an experimental cage (27 × 16 × 23 cm) containing 5 cm of fine sawdust during 30 min per day; on the fourth day, the cage was conditioned with an acrylic prod in a wall (2 cm above the bed), which was connected to a stimulator of constant current (model 5806, LaFayette Instruments, Inc., IN, USA). Rats were individually tested during 10 min: when a rat touched the prod it received one or more electric shocks (0.3 mA) and responded to it

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