Effects of chronic Tamoxifen treatment in the hypothalamic circuitry that regulates female sexual behaviour

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Introduction

Breast cancer is a disease responsible for high rate of morbidity and death in women. One very common therapy to treat estrogen-dependent breast cancer tamoxifen (TAM), an anti-estrogen that have been proven to improve the clinical outcomes of this disease [1-3]. In this way, the majority of women diagnosed with breast cancer can be expected to live longer [1-3]. However, as an endocrine modulator, TAM therapy has been shown to promote a wide spectrum of side effects, such as diminished libido [4-6]. The increased survival rate associated with TAM treatment will be linked to increased risk of deleterious side effects. Because nowadays it is offered a 5 years prophylactic TAM therapy to woman with high risk of having breast cancer, the impact of endocrine therapy on the quality of life is extremely important. Although previous studies have shown several relevant side effects related with TAM treatment, the mechanisms underlying this event are currently unknown. With the identification of the effects of long-term TAM therapy in biochemical plasticity of ovarian hormone receptors in the preoptic area and Mediobasal hypothalamus, both areas that control the proceptive and the receptive component of the female sexual behavior [7,8], this study aimed to improve the knowledge about the behavioral outcomes associated with TAM therapy.

Material and Methods

TAM was administrated daily, for three months, to normally cycling young female Wistar rats in a dose known to mimic the one used by woman in hormone therapy. In order to identify the effects of TAM in the estrous cyclicity, vaginal lavage was done daily and the uterine weight and hormone ovarian levels were determined upon sacrifice. The brain areas were studied using immunohistochemistry for the detection of the expression of estrogen (ER) and progesterone receptors (PR).

Results

Since Estrus was the phase of the cycle at the nadir of both ovarian hormone levels, all results are presented as a percentage of Estrus values (considering Estrus 100%).

The results show that TAM inhibits the cycling fluctuation of estradiol and progesterone (Fig 1).

Tamoxifen acts as an estrogen by increasing the amount of ERs in the VMN (Fig. 2) and as an antagonist by counteracting the action of estradiol in the expression of PR in the VMN (Fig. 2) and of both receptors in the POA (Fig. 3).

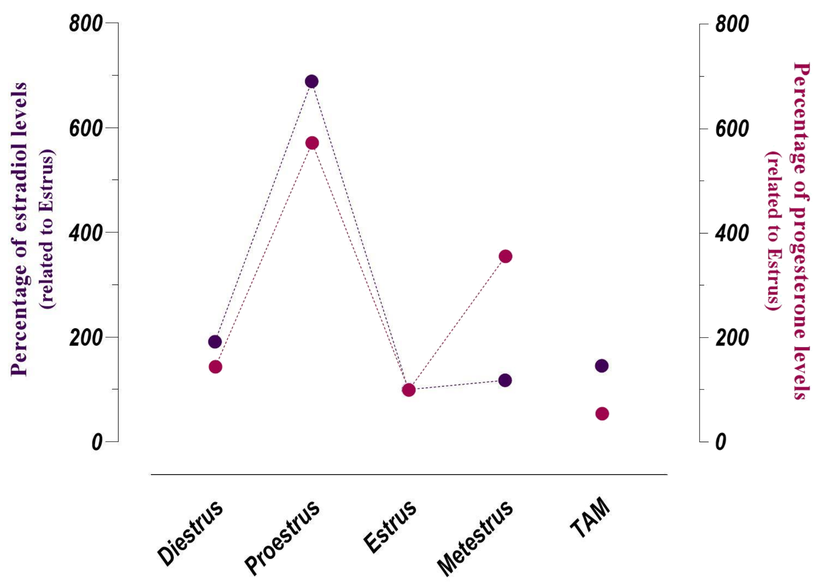

Fig. 1

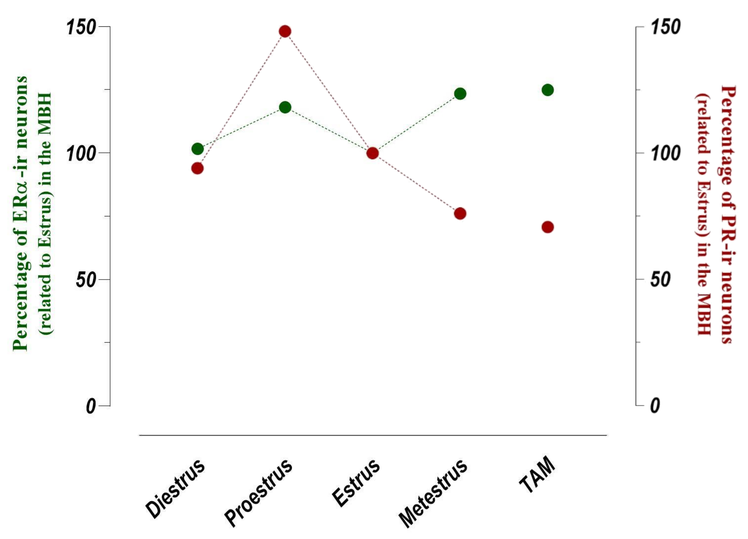

Fig. 2

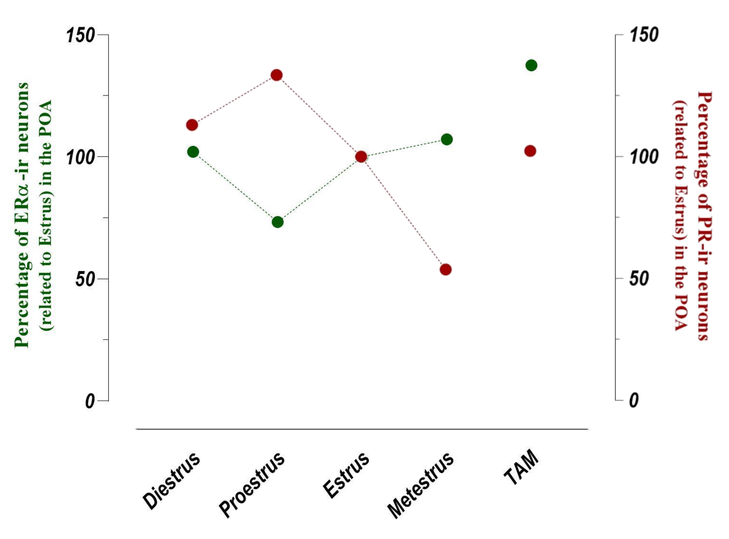

Fig. 3

Discussion

It was previously shown a relation between the levels of ovarian hormones and the ability of the female rat to display sexual behavior [7,8]. The same causality was seen for the induction ERalfa-dependent expression of PRs and that the MBH plays a facilitative, while the POA plays an inhibitory action in the promotion of the behavior [7,8]. Presented results suggests that the seen changes in the expression of both receptors in the VMN and POA may be a possible mechanism of TAM action in the inhibition of the sexual response

References

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Acknowledgements / Funding

National Funds through FCT - Fundação para a Ciência e a Tecnologia trough Project PEst-OE/SAU/UI0121/2011; FEDER through the operation POCI-01-0145-FEDER-007746; Programa Operacional Competitividade e Internacionalização – COMPETE2020; National Funds through FCT - Fundação para a Ciência e a Tecnologia within CINTESIS, R&D Unit (UID/IC/4255/2013).