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Influence of estradiol administration on estrogen receptors of nasal mucosa: an experimental study on guinea pigs☆

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KEYWORDS
Nasal mucosa;
Estrogens;
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Abstract
Introduction: Some clinical trials revealed a correlation between increased serum estrogen and nasal symptoms or inflammatory changes in nasal mucosa. Estrogen receptors tend to be controlled by a negative feedback, to avoid a deleterious stimulus over several body functions while in hyperestrogenic periods. This study proposes a hypothesis where mechanisms regulating expression of estradiol receptors in nasal mucosa are absent in some patients, and their concentration remains steady even in periods of high serum hormonal concentration, potentially leading to local estrogenic symptoms in nasal mucosa.
Study design: This was an experimental prospective study.
Aim: To determine whether estrogen levels induce the reduction of the number of estrogen receptors in the nasal mucosa.
Methods: In the present study, 30 adult male guinea pigs were subjected to a biopsy of the middle nasal turbinate and received 0.5 mL of estradiol cypionate intraperitoneally for 30 consecutive days. Afterwards, samples from contralateral middle turbinate were obtained. Immunohistochemical analysis of estrogen receptors were performed pre- and post-treatment.
Results: The post-treatment group showed reduction of receptor expression when compared to the pre-treatment group. (p = 5.2726-5).
Conclusion: A reduction in the expression of the nasal estrogen receptor was observed after 30 days of estradiol administration.

PALAVRAS-CHAVE
Mucosa nasal;
Estrogênios;
Imunoistoquímica

A influência da administração de estradiol nos receptores de estrógeno da mucosa nasal: estudo experimental em cobaias

Resumo
Introdução: A literatura indica uma correlação entre estrogênio elevado no soro e sintomas nasais ou alterações inflamatórias na mucosa nasal. Os receptores de estrogênio tendem a ser controlados por retroalimentação negativa, para evitar um estímulo nocivo sobre as diversas funções corporais em períodos de hiperestrogenismo. Propomos uma hipótese em que os mecanismos que regulam a expressão de receptores de estradiol na mucosa nasal estão ausentes em alguns pacientes, e a sua concentração permanece estável mesmo em

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períodos de elevada concentração sérica hormonal, o que pode conduzir a sintomas locais na mucosa nasal.
Desenho do estudo: estudo prospectivo experimental.
Objetivo: Determinar se altos níveis de estrogênio induzem à redução no número de receptores de estrogênio na mucosa nasal.
Material e método: Trinta cobaias foram submetidas à biópsia da concha nasal, recebendo 0,5 ml de cipionato de estradiol por via intraperitoneal por trinta dias consecutivos. Em seguida foram obtidas amostras da concha nasal contralateral. As análises imuno-histoquímicas dos receptores de estrógeno foram realizadas antes e depois da hormonioterapia.
Resultados: O grupo pós-tratamento mostrou uma redução da expressão dos receptores (p = 5,2726-5).
Conclusão: Redução na expressão do receptor de estrogênio nasal foi encontrada após trinta dias de administração de estradiol.

Introduction

Rhinitis may be classified into two groups: allergic and non-allergic. The non-allergic group includes hormonal rhinitis, in which inflammatory alterations in nasal mucosa are associated to elevated hormone levels, such as hyperestrogen states occurring during pregnancy, menstruation, or with use of hormonal contraception.[1-3]

Hormonal rhinitis has been the focus of clinical trials since the 19th century, when several authors published studies correlating hormonal fluctuations with nasal symptoms. Many authors[4-7] carried out experimental studies disclosing histological and histochemical changes in nasal mucosa in response to changes in the concentration of serum estrogen.

Some clinical trials[8-16] observed a correlation between increased serum estrogen and nasal symptoms or inflammatory changes in nasal mucosa on clinical and laboratory exams. Conversely, other studies, such as those by Mabry,[17] by Ellegard,[18,19] by Bende and Gredmark,[20] and by Salaroli et al.[21], failed to confirm this correlation.

Toppozada et al.[22-24] observed histological and histochemical alterations in the human nasal mucosa of women who were pregnant or using contraceptive pills, compared with a control group. Caruso et al.[12] and Nappi et al.[25] noticed that the vaginal and nasal respiratory epithelium exhibited the same histologic aspects in the respective phases of the menstrual cycle and during menopause.

The first estrogen receptor (ER) to be described, alpha (ERα), was isolated by Elwood Jensen in 1958. In 1996, Enmark and Gustafsson[26] discovered a second type of receptor, beta (ERβ). Theories proposed about the physiological functions of these two isoforms implicate selective action of estrogen in different tissues.

Thus, research into the two receptors subtypes has been conducted in a range of different organs and tissues. ERβ was found in the prostate, ovaries, testicles, uterus, hypophysis, bladder, lungs, salivary glands, oral mucosa, thymus, adrenals, olfactory tract, central nervous system, heart, kidneys, and in cells of the immunologic system.[27] ERα was found at highest concentrations in the uterus, vagina, and breasts;[28] however, few studies investigating ERs in nasal mucosa are available.

The mucosa of lower nasal turbinates in women with chronic rhinopathy was investigated by immunohistochemistry for ERs, which were dectected in the cytoplasm of glandular epithelium cells.[29,30] Millas[31] employed immunohistochemistry to study estrogen ERα and ERβ in the mucosa of lower nasal turbinates of normal subjects. All 11 cases studied (five women and six men) presented ERα and ERβ (predominantly the latter) in the cytoplasm of glandular epithelial cells of the lamina propria. When studying individuals with chronic rhinopathy, Shirasaki et al.[32] observed ERα in the nuclei of mastocytes, and ERβ in nuclei of cells of the glandular epithelium of the lamina propria.

Controversy remains over the site and function of receptors for estrogen in nasal mucosa. Millas et al.[33] assessed the influence of oral contraceptives on the distribution and density of ERs in the nasal mucosa of women, and observed that those using contraceptive pills had a lower number of receptors in the lamina propria.

The expression of receptors in cells is dynamic and regulated mainly by the concentration of their cognate ligands. Reports by Jensen and Gorski describing the regulation of ER concentration observed that estrogen treatment led to a decrease in cytosolic ERs, based on the reduction in specific binding to 17β-estradiol. Given that the receptors are the key determinants of the action of several hormones in target cells, and that evidence points to a possible estrogen activity in nasal mucosa, the mechanism of down-regulation may explain the fact that, in general, women do not present significant nasal effects when there is marked variation in their sexual hormones.

Inversely, a hypothesis may be proposed that mechanisms regulating receptors expression are absent and that their concentration remains steady even during high hormonal concentration, potentially leading to local estrogenic symptoms in nasal mucosa. This study aimed to determine whether an elevation in circulating estrogen levels influences the concentration of ERs in guinea pig nasal mucosa.

Materials and methods

A prospective study of nasal mucosa samples from 30 adult male guinea pigs weighting between 300 g and 400 g was performed.