Estrogen receptors alpha and beta in non-target organs for hormone action: review of the literature

Millas, I.[1] and Liquidato, BM.[2]*

[1]Otorhinolaryngology Department of Santa Casa de São Paulo, School of Medical Sciences, São Paulo, SP, Brazil
[2]Morphology Department of Santa Casa de São Paulo, School of Medical Sciences, São Paulo, SP, Brazil
*E-mail: bmliqui@ig.com.br

Abstract

Estrogens are known to influence genetic expression by interfering in cell growth and differentiation through different mechanisms, both in organs associated with reproduction and in other areas. Recently, the number of studies investigating these receptors in different tissues by means of the immunohistochemical method has been increasing. Another method that has also been used recently is investigation of the expression of RNA-m at the specific receptors by means of PCR. The effects of estrogen have been analyzed in relation to a significant number of tissue types that are not associated with reproduction, for example bones and the cardiovascular, gastrointestinal, immunological and central nervous systems. Hence, the aim of the present study was to review the literature on estrogen receptors in non-target organs for the action of this hormone, i.e. in organs that are not associated with reproduction.

Keywords: receptors, estrogen, estrogens, immunohistochemistry, polymerase chain reaction, hormones.

1 Introduction

Estrogens are known to influence genetic expression by interfering in cell growth and differentiation through different mechanisms, both in organs associated with reproduction and in other areas (GRUBER, JC., GRUBER, DM., GRUBER, IML. et al., 2004).

Recently, with the advent of monoclonal antibodies against specific estrogen receptors, the number of studies investigating these receptors in different tissues by means of the immunohistochemical method has been increasing. Another method that has also been used recently is investigation of the expression of RNA-m at the specific receptors by means of polymerase chain reaction (PCR), through which it can be assessed whether the receptor is functional, i.e. whether there is genetic control and cell function control (CIOCCA and ROIG, 1995).

Estrogen receptors belong to the superfamily of nuclear receptors for transcription factors. The binding of estrogen to its receptor depends on co-activator factors that help the action of the receptors towards cell DNA and on co-repressor factors that cause difficulty. Following this interaction, estrogen receptors change from monomers to dimers and couple in specific regions of the cell DNA where there may or may not be transcription of genes involved in cell division, differentiation, homeostasis and metabolism (PAVAO and TRAISH, 2001). Certain routes in which estrogen receptors may be activated independent of a hormonal ligand have also been described (GRUBER, JC., GRUBER, DM., GRUBER, IML. et al., 2004).

Jensen (1958) discovered the first estrogen receptor, which was named estrogen receptor alpha. In 1996, using the technique of cloning the DNAc of estrogen receptors, a second estrogen receptor named estrogen receptor beta was discovered (KUIPER, ENMARK, PELTO-HUIKKI et al., 1996). This gave rise to several other studies on these two isoforms of estrogen receptors, which have high affinity and specificity in humans. This phenomenon enables selective action by the hormone on different tissues (KUIPER, ENMARK, PELTO-HUIKKI et al., 1996; MOSSELMAN, POLMAN, DIJKEMA et al., 1996; PAECH, WEBB, KUIPER et al., 1997). Estrogen receptors alpha and beta present different binding affinities with the hormone and the respective co-repressor and co-activator factors (GRUBER, JC., GRUBER, DM., GRUBER, IML. et al., 2004). The alpha receptor generally has greater transcriptional activity than shown by the beta receptor (KLINGE, 2001).

The importance of investigating estrogen receptors in non-target organs relates to achieving better understanding of the action of this hormone on tissues that until recently were neglected regarding the action of this hormone. Estrogen acts both in men and in women, and it is known that it can cause cell modifications when it reacts with its respective receptors (KUIPER, ENMARK, PELTO-HUIKKI et al., 1996).

Thus, the effects of estrogen have been analyzed in relation to a significant number of tissue types that are not associated with reproduction, for example bones and the cardiovascular, gastrointestinal, immunological and central nervous systems. A large number of diseases are associated with changes in estrogen production and/or the hormonal cell response, such as osteoporosis, breast cancer, endometrial cancer, prostate cancer and atherosclerosis (ENMARK and GUSTAFSSON, 1999). In 2000, using the immunohistochemical method, Taylor and Al-Azzawi (2000) found that estrogen receptor beta was present in cells in the esophagus, lungs, small intestine, heart, brain, thyroid,

stomach, rectum, endothelium and smooth musculature of blood vessels.

Hence, the aim of the present study was to review the literature on estrogen receptors in non-target organs for the action of this hormone, i.e. in organs that are not associated with reproduction.

2 Material and method

This study consisted of a review of the literature over the last ten years, indexed in Pubmed, Medline and Scielo, covering papers relating to estrogen receptors, immunohistochemistry and steroid hormones.

3 Results

3.1 Central nervous system

Watanabe, Inoue, Hiroi et al. (1999) detected estrogen receptors alpha and beta in various regions of the brains of rats through an experimental study.

Ishunina, Kruijver, Balesar et al. (2000) used the immunohistochemical method in 2000 to evaluate the expression of estrogen receptors alpha and beta in cells of the human supraoptic nucleus, in order to assess the possible inhibitory effect of estrogen on the production of arginine vasopressin, mediated by its receptors. Estrogen receptors alpha and beta were found to be present in the nucleus and cytoplasm of neurons of the supraoptic nucleus in individuals of both sexes, with differences in predominance between the receptor types that depended on age and sex. Young women showed greater numbers of neurons with nuclear and cytoplasmic staining for the beta receptor.

Milner, McEwen, Hayashi et al. (2001) carried out an experimental study using immunohistochemistry in 2001, to investigate estrogen receptor alpha in the hippocampus of rats. Estrogen seems to change the neuroprotective effects relating to Alzheimer's disease. The effect of estrogen on the hippocampus is given through the alpha receptors. Studies have suggested that estrogen, through estrogen receptor alpha, diminishes GABAergic inhibition and thereby increases the formation of new dendrites. Estrogen receptor alpha has been found both in nuclei and in extra-nuclear regions, thus suggesting that estrogen can have rapid non-genomic effects on cell membranes, mediated by the receptor, thereby activating G proteins and consequently, second messenger activity. Another possibility is stimulation of the second messenger system by means of increased intracellular calcium levels, through these receptors.

Ostlund, Keller and Hurd (2003) published a study that correlated the expression of estrogen receptors and neuropsychiatric disorders. The alpha receptor is present in the amygdale and hypothalamus, thus suggesting that there is estrogen modulation in autonomic, neuroendocrine and emotional functions. On the other hand, the beta receptor is predominant in areas such as the hippocampus and thalamus, thus suggesting the presence of action relating to cognition, non-emotional memory and motor functions.

Nassif, Cimarosti, Zamin et al. (2005) studied the neuroprotective mechanisms of estrogen in relation to cerebral ischemia. Through the estrogen receptors, this hormone can change the balance of the genes responsible for expression of pro and anti-apoptotic proteins, stimulate the synthesis of growth factors and their receptors, and can also interact with signal transduction routes, thereby leading to neuroprotection.

According to Tiwari-Woodruff, Morales, Lee et al. (2007), estrogen receptors alpha and beta act synergically on some tissues and antagonistically on others. In the nervous system, it can be seen that the alpha receptor has anti-inflammatory activity, while the beta receptor has a neuroprotective effect through reducing demyelinization and preserving axons.

3.2 Cardiovascular system

Simoncini, Fornari, Mannella et al. (2002) described non-genomic effects caused by estrogen receptor alpha on the vascular system, which gave rise to vasodilation and favored the release of nitric oxide.

With regard to vascular contractility, estrogen has been shown to have rapid vasodilatory effects on small arteries in experimental studies. Thus, Montgomery, Shaw, Pantelides et al. (2003) observed that selective agonists for estrogen receptors alpha and beta caused acute relaxation of the mesenteric arteries of rats, especially the agonist for estrogen receptor beta.

Pelzer, Loza, Hu et al. (2005) reported that because of the difference in the development of cardiovascular diseases between men and women, several studies were being conducted to investigate estrogen receptors in that system. In the heart, both receptors are expressed in cardiac muscle cells, fibroblasts and endothelial cells, where they may have redundant, non-redundant or occasionally opposite biological effects. In the vascular system, the alpha receptor (and not the beta receptor) inhibits the formation of the neointima. On the other hand, the beta receptor is associated with regulation of arterial pressure, given that guinea pigs without this receptor develop hypertension. Thus, through an experimental study, these authors observed that absence of the beta receptor in rats increased mortality and clinically and biochemically worsened the markers for heart failure.

Christian, Liu, Harrington et al. (2006) observed that the beta receptor predominated in the coronary arteries and correlated with coronary calcification. Thus, this indicated that increased expression of the beta receptor might favor the process of atherosclerosis.

Using the immunohistochemical, Reverse transcriptase-PCR (RT-PCR) and Western blot methods, Foresta, Zuccarello, Biagioli et al. (2007) found estrogen receptor alpha (and not beta receptors) in progenitor endothelial cells. This suggested that estrogen might stimulate proliferation of these cells in vitro.

3.3 Gastrointestinal tract

Because of several studies that had reported that the colon was one of the organs influenced by estrogen through the beta receptor, Wada-Hiraike, Imamov, Hiraike et al. (2006) carried out an experimental study in 2006, on the role of estrogen in relation to the colon epithelium. They observed that the beta receptor had an important role in organizing and maintaining the cell architecture of the colon epithelium, through increasing the numbers of cell adhesion molecules.

3.4 Oral mucosa and salivary glands

Leimola-Virtanen, Salo, Toikkanen et al. (2000) evaluated 10 postmenopausal women and 20 healthy young women. They found that nonspecific estrogen receptors were present, by means of RT-PCR and immunohistochemistry on biopsies from the oral mucosa and salivary glands. The presence of estrogen receptors was detected by means of RT-PCR in all samples, but none of the cases presented a positive immunohistochemical reaction. The expression of RNA-m by the estrogen receptors was lower in the postmenopausal women than in the young women.

In the same year, Yih, Richardson, Kratochvil et al. (2000) performed the immunohistochemical method to investigate nonspecific estrogen receptors in gingival biopsy samples from 24 women and one man with chronic nonspecific gingivitis. A positive immunohistochemical reaction for estrogen receptors was detected in epithelial cells (including in the cytoplasm) and in connective tissue cells such as fibroblasts and endothelial cells.

Desquamative gingivitis is more common in women and the severity of the gingival inflammation increases during pregnancy, including with the risk that gingival pyogenic granuloma might appear. On the other hand, after the menopause, the gingival epithelium becomes hypotrophic. Thus, Välimaa, Savolainen, Soukka et al. (2004) used immunohistochemistry to investigate estrogen receptors alpha and beta in gingival tissue and the smaller salivary glands of men and women who underwent oral surgery. Beta receptors were found in the nuclei of epithelial cells in the gingiva and in the nuclei and cytoplasm of glandular epithelial cells of the salivary glands. On the other hand, alpha receptors were not found in any of the samples analyzed.

Estrogen also regulates the expression of phenotypes of osteoblasts in the cells of the periodontal ligament and may help in regenerating this tissue through its receptors. Thus, Tang et al. (2008) found both receptors in the nuclei of cells of the periodontal ligament, with predominance of beta receptors. This study suggests that this receptor may participate actively in the process of osteogenic differentiation in the cells of the human periodontal ligament, in men and women.

3.5 Genitourinary tract

Because cystitis is more common in women, Bjorling and Wang (2001) used the immunohistochemical method in 2001, to investigate the mucosa of the urinary bladder in rats. They found that estrogen receptors alpha and beta were present, with predominance of beta receptors. They put forward the theory that estrogen might influence the course of neurogenic inflammation through interaction with pain mediators such as the neural growth factor, thereby making the bladder more sensitive to nociceptive stimuli.

3.6 Respiratory system

Zhao, McKerr, Dong et al. (2001) carried out an immunohistochemical study on estrogen receptors (nonspecific) in nasal polyps. The literature suggested that age and oscillations in sex hormones might exacerbate the symptoms of asthma. Thus, these authors observed that these receptors were only present in mast cells and not in other inflammatory cells in the cases studied, which may suggest that estrogen has an inflammatory effect on the airways.

Also in 2001, Bowser and Riederer (2001) carried out an immunohistochemical study to investigate estrogen receptors (nonspecific) and progesterone receptors in the mucosa of the inferior nasal turbinates of 40 women. They found positive staining for estrogen receptors in the cytoplasm of serous cells of the glandular epithelium and in cells of the secretory ducts. This study was conducted on both users and nonusers of hormonal contraceptives, and no statistically significant difference was found between these two groups.

Nappi, Sardo, Guerra et al. (2003) used the immunohistochemical method to investigate estrogen receptor alpha in samples from the inferior nasal turbinates of 24 postmenopausal women, of whom 12 were using hormone replacement therapy and 12 were not (control group). A positive immunohistochemical reaction for estrogen receptor alpha was detected in the cells of the seromucous glands of the lamina propria and around the venules. The expression of these receptors was significantly lower in the postmenopausal women who were not receiving hormone replacement therapy than in the other group.

Shirasaki, Watanabe, Kanaizumi et al. (2004) carried out a study using immunohistochemistry and RT-PCR to investigate estrogen receptors (alpha and beta), androgen, progesterone and glucocorticoids in the mucosa of the inferior nasal turbinates of seven patients with chronic rhinopathy who underwent turbinectomy. Four were male and three were female, and their ages ranged from 16 to 55 years. Through RT-PCR, mRNA of estrogen receptor alpha was detected in all the cases and estrogen receptor beta in five of the cases. Through immunohistochemistry, estrogen receptor alpha was observed in the nuclei of interstitial cells, particularly mast cells, and in the cytoplasm of epithelial cells. On the other hand, estrogen receptor beta was found in the nuclei of cells of the glandular epithelium of the lamina propria.

Philpott, Wild, Wolstensholme et al. (2008) used the immunohistochemical method on paraffin-embedded material to investigate estrogen receptors alpha and beta and progesterone receptors in biopsy samples from the mucosa of the inferior nasal turbinates of 25 patients with rhinitis who underwent otorhinolaryngological surgical procedures. Among these patients, 16 were male. The age range was from 18 to 68 years. None of the biopsies showed positive reactions for estrogen receptor alpha or for progesterone receptors. Estrogen receptor beta was present in 24 out of the 25 samples, in the cells of the glandular epithelium of the lamina propria and in cells of the lamina propria and venules. There were no statistically significant differences between the groups of men and women, atopic and non-atopic individuals or smokers and nonsmokers.

The differences between men and women regarding pulmonary diseases led Ivanova, Mazhawidza, Dougherty et al. (2009) to examine normal epithelial cells from the human bronchial mucosa. Alpha and beta receptors were found in the cytoplasm, nuclei and mitochondria. These authors also compared the estrogen response in normal and cancerous cells and observed that the response of the epithelial cells of the bronchial mucosa to estrogen did not depend on sex. However, they found that estrogen sensitivity could be acquired during carcinogenesis, thereby explaining

the estrogen transcriptional responses seen in cases of pulmonary adenocarcinoma among women.

3.7 Eyes

The incidence of glaucoma is greater among postmenopausal women, thus suggesting that estrogen may influence the secretion/reabsorption balance of the aqueous humor. Fuchsjager-Mayrl, Nepp, Schneeberger et al. (2002) investigated estrogen receptors alpha and beta in samples from the conjunctiva of ten women of reproductive age who underwent ophthalmic surgery, by means of RT-PCR and Western blot. Both receptors were detected, thus indicating possible action by estrogen on the conjunctiva, which could influence changes in allergic response and in the maturation of caliciform cells and conjunctival epithelial cells.

3.8 Internal ear

In an experimental study on the ear, Meltser, Tahera, Simpson et al. (2008) found that estrogen acted on the auditory system to protect it against acoustic trauma. Using immunohistochemistry and Western blot, they detected beta receptors in the cochlea in both sexes, in the nuclei of the internal and external ciliated cells and in the nuclei of cells of the spiral ganglion. These data suggest that estrogen receptor beta mediates neuroprotection, involving a neurotrophic factor derived from the brain.

3.9 Sweat glands

In 2004, using the immunohistochemical method, Beier, Ginez and Schaller (2005) found estrogen receptor beta in secretor epithelium of the apocrine sweat glands of the human axilla. The results from this study establish a possible link between estrogen action and induction of pheromone production in the axillary apocrine glands.

4 Conclusion

Hormones are molecules that communicate with cells that are distant from the organ where they are synthesized and are carried by means of the blood stream. They function as signaling molecules that act on target cells, i.e. cells that express specific receptors. They thus coordinate the growth, differentiation and cell metabolism in different organs and tissues (DARNELL, 1995).

In this way, although estrogen is a hormone that was initially thought to have a role only in the reproductive organs, it may influence cell functions through its receptors in difference types of tissue. These tissues may or may not be associated with the principal function of estrogen, i.e. reproduction, as described in previous studies.

Over the last few years, many studies have been conducted on different organs and tissues, in relation to the different estrogen receptors. With the discovery of the second type of estrogen receptor, the beta receptor, there has been an increase in the interest in studies on the action of this hormone in organs that are primarily said not to be targets for hormonal action. It has been postulated that the existence of these two isoforms would make it possible for estrogen to have selective action in different types of tissue (PAVAO and TRAISH, 2001), because of differences in hormonal binding properties and/or target gene activation function (KUIPER, ENMARK, PELTO-HUIKKI et al., 1996).

Through experimental studies in 1997, Kuiper, Carlsson, Grandien et al. (1997) observed that alpha receptors were found in the epididymis, prostate, testicles, hypophysis, ovaries, uterus, kidneys and adrenal gland. On the other hand, beta receptors were found also in organs such as the bladder, lungs, thymus gland, olfactory tract, central nervous system and heart. Likewise, in a similar study in 1997, Brandenberger et al also observed that both receptors were expressed abundantly in the reproductive system and that beta receptors were also present in high concentrations in tissues that did not produce and were not dependent on estrogen.

Beta receptors were also found in an experimental study using RT-PCR, in many tissue types including the central nervous system, cardiovascular system, immunological system, urogenital tract, gastrointestinal tract, kidneys and lungs. Alpha receptors predominated in tissue types that were associated with reproduction, such as the breasts, uterus and vagina. The different biological activities of these two isoforms can be explained by differences in their distribution and structure, which indicates that variations in the recruitment of their respective transcriptional factors, co-activators or co-repressors may occur (PAVAO and TRAISH, 2001).

Beta receptors have been shown to have greater predominance in organs not associated with reproduction. However, what seems to characterize the expression of estrogen in the different organs is the balance between the concentrations of their receptor subtypes and the recruitment (or lack of recruitment) of the co-activator and co-repressor factors for each subtype, for genetic expression. This recruitment varies according to the tissue type. For example, as cited earlier, one receptor type or another predominates in certain regions of the brain and the same receptor may or may not trigger genetic transcription, depending on its location. Furthermore, the location within the cell may also influence the type of response, as in the case of cytoplasmic receptors that are responsible for rapid non-genomic effects.

It can therefore be seen that estrogen has important functions in a variety of organs, mostly mediated through its receptors, and that the response depends on each tissue type. The effects of this hormone go well beyond the limits of reproductive activity, and they have been the subject of studies aimed at achieving better histophysiological understanding and therapeutic intervention. Thus, new and promising paths for research have been shown.

References

BEIER, K., GINEZ, I. and SCHALLER, H. Localization of steroid hormone receptors in the apocrine sweat glands of the human axilla. Histochemistry and Cell Biology. 2005, vol. 123, p. 61-65.

BJORLING, DE. and WANG, ZY. Estrogen and neuroinflammation. Urology. 2001, vol. 57, p. 40-46.

BOWSER, C. and RIEDERER, A. Detection of progesterone receptors in connective tissue cells of the lower nasal turbinates in women. Laryngorhinootologie. 2001, vol. 80, p. 182-186.

CHRISTIAN, RC., LIU, PY., HARRINGTON, S. et al. Intimal Estrogen Receptor (ER) beta, but not ERalpha expression, is correlated with coronary calcification and atherosclerosis in pre and postmenopausal women. Journal of Clinical Endocrinology and Metabolism. 2006, vol. 91, p. 2713-2720.

CIOCCA, DR. and ROIG, LMV. Estrogen receptors in human nontarget tissues: biological and clinical implications. Endocrine Reviews. 1995, vol. 16, p. 35-62.

DARNELL, JE. Molecular cell biology. 3 ed. New York: Scientific American Books, 1995.

ENMARK, E. and GUSTAFSSON, JA. Oestrogen receptors: an overview. Journal International Medicine. 1999, vol. 246, p. 133-138.

FORESTA, C., ZUCCARELLO, D., BIAGIOLI, A. et al. Oestrogen stimulates endothelial progenitor cells via oestrogen receptor-α. Clinical Endocrinology. 2007, vol. 67, p. 520-525.

FUCHSJAGER-MAYRL, G., NEPP, J., SCHNEEBERGER, C. et al. Identification of estrogen and progesterone receptor mRNA expression in the conjunctiva of premenopausal women. Investigative Ophthalmology & Visual Science. 2002, vol. 43, no. 9, p. 2841-2844.

GRUBER, JC., GRUBER, DM. and GRUBER, IML. Anatomy of the estrogen response element. Trends in Endocrinology and Metabolism. 2004, vol. 15, no. 2, p. 73-78.

ISHUNINA, TA., KRUIJVER, FPM., BALESAR, R. et al. Differential expression of estrogen receptor α and β immunoreactivity in the human supraoptic nucleus in relation to sex and aging. The Journal of Clinical of Endocrinology of Metabolism. 2000, vol. 85, p. 3283-3291.

IVANOVA, MM., MAZHAWIDZA, W., DOUGHERTY, SM. et al. Activity and intracellular localization of estrogen receptors alpha and beta in human bronchial epithelial cells. Molecular and Cellular Endocrinology. 2009, vol. 305, p. 12-21.

JENSEN, EV. On the mechanism of estrogen action. Perspectives in Biology and Medicine. 1962, vol. 6, p. 47-59.

KLINGE, CM. Estrogen receptor interaction with estrogen response elements. Nucleic Acids Research. 2001, vol. 29, p. 2905-2919.

KUIPER, GG., ENMARK, E., PELTO-HUIKKI, M. et al. Cloning of a novel receptor expressed in rat prostate and ovary. Proceedings of the National Academy of Sciences. 1996, vol. 3, p. 5925-5930.

KUIPER, GGJM., CARLSSON, B., GRANDIEN, K. et al. Comparison of the ligant binding specificity and transcript tissue distribution of the estrogen receptors α and β. Endocrinology. 1997, vol. 138, p. 863-70.

LEIMOLA-VIRTANEN, R., SALO, T., TOIKKANEN, S. et al. Expression of Estrogen Receptor (ER) in oral mucosa and salivary glands. Maturitas. 2000, vol. 36, p. 131-137.

MELTSER, I., TAHERA, Y., SIMPSON, E. et al. Estrogen receptor β protects against acoustic trauma in mice. The Journal of Clinical Investigation. 2008, vol. 118, p. 1563-1570.

MILNER, TA., MCEWEN, BS., HAYASHI, S. et al. Ultrastructural evidence that hippocampal alpha estrogen receptors are located at extranuclear sites. The Journal of Comparative Neurology. 2001, vol. 429, p. 355-371.

MONTGOMERY, S., SHAW, L., PANTELIDES, N. et al. Acute effects of oestrogen receptor subtype-specific agonists on vascular contractility. Bristish Journal Pharmacology. 2003, vol. 139, p. 1249-1253.

MOSSELMAN, S., POLMAN, J. and DIJKEMA, R. ER beta: identification and characterization of a novel human estrogen receptor. Federation of European Biochemical Societies Letters. 1996, vol. 392, p. 49-53.

NAPPI, C., SARDO, AS., GUERRA, G. et al. Functional and morphologic evaluation of the nasal mucosa before and after hormone therapy in postmenopausal women with nasal symptoms. Fertility and Sterility. 2003, vol. 80, p. 669-671.

NASSIF, MC., CIMAROSTI, HI., ZAMIN, LL. et al. Estrógeno versus isquemia cerebral: hormônio feminino como agente neuroprotetor. Infarma. 2005, vol. 17, p. 57-60.

OSTLUND, H., KELLER, E. and HURD, YL. Estrogen receptor gene expression in relation to neuropsychiatric disorders. Annals of the New York Academy of Science. 2003, vol. 1007, p. 54-63.

PAECH, K., WEBB, P., KUIPER, GGJM. et al. Differential ligand activation of estrogen receptors ERα and ERβ at AP1. Sites Science. 1997, vol. 277, p. 1508-1510.

PAVAO, M. and TRAISH, AM. Estrogen receptor antibodies: specificity and utility in detection, localization and analyses of estrogen receptor alpha and beta. Steroids. 2001, vol. 66, p. 1-16.

PELZER, T., LOZA, PAA., HU, K. et al. Increased mortality and aggravation of heart failure in estrogen receptor: knockout mice after myocardial infarction. Circulation. 2005, vol. 111, p. 1492-1498.

PHILPOTT, CM., WILD, DC., WOLSTENSHOLME, CR. et al. The presence of ovarian hormone receptors in the nasal mucosa and their relationship to nasal symptoms. Rhinology. 2008, vol. 46, p. 221-225.

SHIRASAKI, H., WATANABE, K., KANAIZUMI, E. et al. Expression and localization of steroid receptors in human nasal mucosa. Acta Oto-Laryngologica. 2004, vol. 124, p. 958-963.

SIMONCINI, T., FORNARI, L., MANNELLA, P. et al. Novel non-transcriptional mechanisms for estrogen receptor signaling in the cardiovascular system. Interaction of estrogen receptor alpha with phosphatidylinositol 3-OH kinase. Steroids, 2002, vol. 67, p. 935-939.

TANG, X., MENG, H., HAN, J. et al. Up-regulation of estrogen receptor -β expression during osteogenic differentiation of human periodontal ligament cells. Journal of Periodontal Research. 2007, vol. 43, p. 311-321.

TAYLOR, AH. and AL-AZZAWI, F. Immunolocalisation of oestrogen receptor beta in human tissues. Journal of Molecular Endocrinology. 2000, vol. 24, p. 145-155.

TIWARI-WOODRUFF, S., MORALES, LBJ., LEE, R. et al. Differencial neuroprotective and anti-inflammatory effects of estrogen receptor (ER) α and ER β ligand treatment. Proceedings of the National Academy of Sciences. 2007, vol. 104, p. 14813-14818.

VÄLIMAA, H., SAVOLAINEN, S., SOUKKA, T. et al. Estrogen receptor-β is the predominant estrogen receptor subtype in human oral epithelium and salivary glands. Journal of Endocrinology. 2004, vol. 180, p. 55-62.

WADA-HIRAIKE, O., IMAMOV, O., HIRAIKE, H. et al. Role of estrogen receptor β in colonic epithelium. Proceedings of the National Academy of Sciences. 2006, vol. 103, p. 2959-2964.

WATANABE, T., INOUE, S., HIROI, H. et al. NMDA receptor type 2D gene as target for estrogen receptor in the brain. Molecular Brain Research. 1999, vol. 63, p. 375-379.

YIH, WY., RICHARDSON, L., KRATOCHVIL, J. et al. Expression of estrogen receptors in desquamative gingivitis. Journal of Periodontology. 2000, vol. 71, p. 482-487.

ZHAO, XJ., MCKERR, G., DONG, Z. et al. Expression of oestrogen and progesterone receptors by mast cells alone, but not lymphocytes, macrophages or other immune cells in human upper airways. Thorax. 2001, vol. 56, p. 205-211.

Received October 13, 2009
Accepted February 3, 2010