Review

UPDATE ON THE MECHANISM OF ACTION OF ESTROGEN RECEPTORS

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RESUMEN

Los mecanismos de acción de los receptores estrogénicos (ER) han sido estudiados debido a sus importantes funciones en el crecimiento celular y la diferenciación de varios órganos y tejidos, relacionados o no con la reproducción. Como en otros procesos regulatorios, los mecanismos de ligados a receptor son cruciales para permitir la acción de los estrógenos que finalmente producirían efectos en el metabolismo celular. Aunque muy estudiados, los mecanismos de acción de los receptores estrogénicos no han sido completamente desentrañados. El presente estudio es una revisión de la literatura sobre el mecanismo de acción de ER-α y ER-β en el cuerpo humano. El conocimiento de la localización y concentraciones de ER en diferentes tejidos es esencial para determinar tratamientos específicos para diferentes patologías, tales como cáncer de mama. Más aún, en tejidos no reproductivos, tales como la mucosa de los cornetes nasales, la presencia de ER-α y ER-β podría explicar las variaciones en la actividad secretora acorde con la variación hormonal. También se consideran las acciones ER neuro-productivas y antinflamatorias en el sistema nervioso central al igual que su función de respuesta alérgica en el epitelio de la conjuntiva y podrían aplicarse a otros estudios referidos al diagnóstico, desarrollo de drogas y el tratamiento de diferentes enfermedades asociados a acciones hormonales.

***Palabras clave**: estrógenos, hormonas, receptores estrogénicos, fisiología, mecanismo*

ABSTRACT

The action mechanisms of estrogen receptors (ER) have been studied due to their important functions in cellular growth and differentiation in several organs and tissues, either or not directly related to reproduction. As in other regulatory processes, the mechanisms of receptor-ligand binding are crucial to enable the action of the estrogen hormone that will ultimately produce effects in the cellular metabolism. Although extensively studied, the mechanisms of action of estrogen receptors are not completely unraveled. The present study is a literature review on the mechanism of action of the ER-α and ER-β in the human body. The knowledge of the location and concentrations of the ER in different tissues is essential to determine specific treatments for different pathologies, such as breast cancer. Moreover, in non-reproductive tissues, such as the nasal conchae mucosa, the presence of ER-α and ER-β may explain the variations in secretory activity of the nasal mucosa according to hormonal variability. ER neuro-protective and anti-inflammatory actions in the central nervous system, as well as its allergic-response function in the epithelium of the conjunctiva are also considered and may apply to other studies concerning the diagnosis, drugs development and clinical treatments of different diseases, related to hormonal actions.

***Keywords:** estrogen, hormones, estrogen receptor, physiology, mechanism*

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INTRODUCTION

Estrogen is a hormone related to cell growth and differentiation in many organs and tissues.
It acts mainly in the regulation of cellular metabolism in different tissues through intranuclear specific protein receptors (Enmark and Gustafsson, 1999; Green et al, 1986; Katzenellenbogen et al, 2000; Kuiper et al, 1996). Estrogen receptors (ER) are homodimeric nuclear receptor protein belonging to the super family of nuclear receptors that bind to liposoluble hormones and interact with specific response elements of DNA. In the absence of hormones, ER remain in the cytoplasm connected to inhibitory proteins, but when attached to their ligands may be taken to the nucleus and activate transcription of target genes. There are two estrogen receptor isoforms, designated as alpha and beta, which have homologous amino acid sequences, particularly differing in the N-terminal region (Enmark and Gustafsson, 1999; Green et al, 1986; Katzenellenbogen et al, 2000; Mosselman, 1996; Paech et al, 1997).
The classical estrogen receptor, which is called alpha, was described in 1962 by Jensen. In 1986 its genetic structure was cloned and defined by Green et al. In 1994, the report of a patient having a genetic mutation with absence of the receptor alpha (ER-α), and showed changes such as osteoporosis and decreased fertility, annulled the hypothesis that the lack of estrogen receptor alpha could be lethal .This fact led to the discovery of a second type of receptor, called beta (ER-β) by Kuiper et al in 1996. Thus, several studies have followed regarding the existence of these two isoforms, with high specificity and affinity in humans, a phenomenon which allows the selective action of the hormone in different tissues (Fchsjauger-mayrl et al, 2002; Gruber et al, 2004; Katzenellenbogen et al, 2000; Kian et al, 2004; Millas et al, 2010; Mosselman, 1996; Soskin and Bernheimer, 1939 ; Taylor and Azzawi, 2000; Tiwari-Woodruff et al, 2007).
In this article we will discuss the mechanisms of action of estrogen receptors, due to its importance in tissue growth, differentiation and metabolism in reproductive organs and in other non- reproductive organs.

MATERIAL AND METHOD

This study consisted of a review of the literature over the last sixteen years, indexed in Pubmed, Medline and Scielo, covering papers relating to estrogen receptors and steroid hormones. The following key words were used in the survey of the literature: estrogen, hormones, estrogen receptor, physiology, and mechanism. Papers were selected for this review regarding as inclusion criteria, those in English language and human researches. And as exclusion criteria papers related to cancer or any proliferative diseases.

RESULTS

Estrogen receptors molecular structure and action

Estrogen receptor α and ER-β are formed by amino acid sequences where the N-terminal region contains one or more transcriptional activation domains, the central region has binding domains with the "zinc fingers" DNA and the C-terminal region has a hormone-dependent binding. The ER-β gene is located on chromosome 14 q 22-24 region and the ER-α gene was mapped on the long arm of chromosome 6 (Green et al, 1986; Gruber et al, 2004; Kuiper et al, 1996; Paech et al, 1997).
When estrogen binds to ER, these monomers become dimers, and are coupled to specific regions of DNA called estrogen and AP-1 sites responsive elements, in which may or may not occur the gene transcription. Both types of receptors can act in different ways in the DNA (Katzenellenbogen et al, 2000; Kuiper et al, 1996; Paech et al, 1997). Studies have shown that changes in the structures of the receptors and their affinity for certain co-activators (enzymes of specific actions) are directly related to their functions. Depending on the dimer formed (receptor + co-activator) the response in the target gene will be different (Amstead et al, 1997; Bernheimer and Soskin, 1942; Jensen, 1962; Kuiper et al, 1996).
The action of the receptors depends on a combination of the receptor, its binding factors and the co-activating or modulating proteins (Katzenellenbogen et al, 2000; Kuiper et al, 1996; Paech et al, 1997). These modulators may have activity that can be agonist and antagonist in the DNA, so the same receptor can express different actions in different cells (Amstead et al, 1997). The activities related to these modulators among different receptor ligans α and β show distinct pharmacological actions on their target genes. For example, drugs such as tamoxifen, tetrahidrocriseno 2-fenilbenzofuram have an agonist activity to α-type receptors, but antagonist to the β, this is due to differences in amino-terminal regions of the receptors

contributing to distinct and specific transcriptional activities (Amstead et al, 1997; Bhagu et al, 2008; Kian et al, 2004; McDonnell, 2004).

Estrogen receptors expression

Literature describes a difference of expression of ER in various tissues. They are present and playing important roles in the reproductive organs and in the others (Caruso et al, 2003; Fchsjauger-Mayrl et al, 2002; Ishunina et al, 2000; Millas et al, 2010; Tiwari-Woodruff et al, 2007) . For example, the ER-β has a higher expression in organs such as brain and adrenal, and ER-α in the uterus and breast. Both are abundantly expressed in reproductive system, while the ER-β is found in high concentrations in tissues that do not produce or are not estrogen-dependent, suggesting that different receptors participate in biochemical processes in different organs. The expression of ER-α is not related to the β and vice versa indicating that they are involved in independent mechanisms of action (Katzenellenbogen et al, 2000; Paech et al, 1997; Taylor and Al-Azzawi, 2000).

The specificity of the receptors' cellular action is associated with different concentrations in these tissues and with different genetic sites related to them in the cells of these tissues (Amstead et al, 1997; Katzenellenbogen et al, 2000; Kian et al, 2004). The actions of these two subtypes and their ligands depend on a ligand-induced conformation for ER-α and ER-β. For example, when estrogen binds to a greater amount of ER-β, the activity of ER-α is inhibited (Bhagu et al, 2008). Moreover, the behavior of each subtype of ER varies within the same tissue. Ishunina et al (2000) observed "up-regulation" of the ER-β and "down-regulation" of α in the same cell group subjected to estrogen, ie, ER have different and specific transcriptional activities, in addition to several tissue responses, due its peculiar concentration and distribution in each tissue. Gruber et al (2004) and Yang et al (2004) also observed that the ER-α has stronger transcriptional affinity, that is affinity in binding to the elements of DNA estrogen response elements, than β.

The selective modulators of estrogen receptors such as tamoxifen and raloxifene show both the properties, estrogenic and antiestrogenic depending on the type of tissue, and show tissue selectivity. The ER-α has a more effective response to estradiol than the ER-β in activation with the estrogen response element present in the DNA. Thus, the ER-β is more effective in the activation of element AP-1 with these modulators, compared to the alpha (Katzenellenbogen et al, 2000; Kian et al, 2004; McDonnell, 2004).

Katzenellenbogen et al, 2000 exemplify the contrary action of the receptors, where tamoxifen has both an agonistic activity with the ER-α and antagonistic activity with ER-β, depending on the receptor. The differences in the amino-terminal regions of ER-α and ER-β contribute to distinct and specific transcriptional activities, as long as both receptors have different distributions and concentrations in the tissues. The respective interactions or activities between these two receptors can generate significant differences in biological tissue responses (Kian et al, 2004).

A repressor protein of estrogen receptor activity (REA) competes with the co-activator of these receptors. REA represents an example of a protein which increases the potency of two inhibitors of ER. For example, the protein quinone reductase (QR), present in the ER, which undergoes an "up-regulation" in the presence of anti-estrogens (hormone of antagonist action to estrogen), suffers a suppression of its activity when bound to estrogen (Amstead et al, 1997; Bhagu et al, 2008). The anti-estrogens have a higher stimulus through QR by ER-β than ER-α. Most genes under the regulation of estrogen receptors seem to suffer an "up-regulation" by estrogen (Bhagu et al, 2008).

Thus, the balance in the performance of ER's tissular functions depends on a complex network of factors; co-activators, co-repressors, estrogen and anti-estrogen concentration and the affinity of each direct transcriptional receptor and the indirect genetic action, repressing or activating response elements in DNA. The knowledge of ER-α and ER-β regarding their location and their concentration in different tissues becomes essential for certain medical treatments as in the case of breast cancer, where, depending on the predominant receptor, selective modulators of ER such as tamoxifen (Kian et al, 2004; McDonnell, 2004) can be used or not.

Estrogen receptors in non reproductive organs

In organs not associated with reproduction, as in the mucosa of inferior nasal conchae the presence of both receptors, ER-α and ER-β was observed in the nucleus and cytoplasm of cells of the glandular epithelium of the lamina propria and respiratory epithelium (Millas et al, 2010; Millas et al 2011; Shirasaki et al 2004). This may explain the hormonal action on the nasal secretory activity and possibly the future use of drugs with hormones to stimulate the nasal secretion in cases of atrophic rhinitis, as it was originally proposed in 1942 by Bernheimer and Soskin, who examined the local effect of estrogen on nasal mucosa for the treatment of patients with

atrophic rhinitis and observed an increase of vascularization and gland secretion of the coated nasal epithelium in the studied cases. In the same line, Caruso et al, 2003, observed better features of the nasal epithelium in women treated with hormones, through the cytology index of cellular maturation.

Similarly, ERs participate in other organs' functions. ERs' different actions in the central nervous system are described by observation that the ER-α has anti-inflammatory activity and beta has neuroprotective activity through reduction of demyelination and axons preserving (Tiwari-Woodruff et al, 2007). In the conjunctival epithelium, the ERs influence the allergic response, since they act in the maturation of goblet cells and cells from the respiratory epithelium as well as influencing the balance of secretion and absorption of aqueous humor, with an important role in the development of glaucoma (Fchsjauger-Mayrl et al, 2002).

This way, as final considerations, we remark the importance of studying the mechanism of action of estrogen receptors in different organs and tissues, which exhibit different functions depending on the expression and the predominance of one or another subtype. As above mentioned, the study of their functions can contribute significantly to the understanding of the pathophysiology of certain diseases and for future advances in treating others, like atrophic and pregnancy rhinitis.

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