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Estrogen receptors: new players in diabetes mellitus

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Diabetes mellitus type 2 is a systemic disease characterized by imbalance of energy metabolism, which is mainly caused by inadequate insulin action. Recent data have revealed a surprising role for estradiol in regulating energy metabolism and opened new insights into the role of the two estrogen receptors, ERα and ERβ, in this context. New findings on gene modulation by ERα and ERβ of insulin-sensitive tissues indicate that estradiol participates in glucose homeostasis by modulating the expression of genes that are involved in insulin sensitivity and glucose uptake. Drugs that can selectively modulate the activity of either ERα or ERβ in their interactions with target genes represent a promising frontier in diabetes mellitus coadjuvant therapy.

Introduction

It is estimated that by the year 2030 ~366 million people will have diabetes mellitus type 2 (DM) (see Glossary) and, despite all the efforts to control it, the number of patients will increase from the present 2.8% to 4.4% of the human population. Obesity, population aging and urbanization are among the main causes of this increase [1].

DM is characterized mainly by disrupted glucose homeostasis with deleterious consequences to many organs such as kidneys, eyes, nervous system and heart and, when untreated, is associated with increased mortality [2]. The etiology of DM is a combination of environmental and genetic factors, but it is believed that the main factor disrupting glucose homeostasis is insulin resistance (i.e. decreased ability of insulin to act on peripheral tissues) [3]. Additionally, insulin resistance is believed to be the main cause of the metabolic syndrome characterized by dyslipidemia, hypertension and visceral obesity, and has become a worldwide health issue [4].

For many years, estradiol (E2) has been considered one of the most important hormones involved in female physiology and reproduction; however, it is now known that its actions are much wider than previously thought. E2 is involved in gene regulation [5,6] and has an important role in several physiological and pathological states in both men and women [7], including glucose homeostasis and insulin resistance.

The use of E2 in post-menopausal women to prevent chronic diseases has been available for decades, but the consequences of estrogen replacement are still controversial. For many years, it has been assumed that E2 decreased vasomotor symptoms, vaginal atrophy, osteoporosis and coronary heart disease (CHD) and increased the incidence of breast cancer. However, recent research has indicated that E2 in post-menopausal women does not affect the incidence of CHD or breast cancer. Moreover, it increases triglyceride levels and the risk of stroke [8].

The existence of conflicting data about E2 actions and the possibility that it might be related to glucose homeostasis and insulin resistance have put E2 replacement therapy under intense investigation.

Estradiol and glucose homeostasis

Most evidence of the association between E2 and glucose homeostasis comes from studies on disease states that are characterized by prominent hormonal fluctuations and disturbances in carbohydrate metabolism. In humans, this association has been debated since 1966, when Wynn and Doar first published their considerations about the effects of contraceptives on lipid and carbohydrate metabolism [9]. Since then, several studies have reported on this potential relationship between E2 and glucose homeostasis in physiological and pathological states such as the menstrual cycle [10,11], gestation [12], gestational diabetes mellitus [13] and polycystic ovarian syndrome (PCOS) [14]. All these states are characterized by variability in E2 levels and some degree of insulin resistance and, consequently, compromised glucose homeostasis.

In animal models, the importance of E2 for glucose homeostasis has been described in mice in which the estrogen biosynthetic enzyme aromatase has been inactivated. Aromatase knockout (ArKO) mice cannot produce E2 [15], and both male and female ArKO mice have reduced glucose oxidation, increased adiposity and insulin levels [16] that might lead to DM in the long term. One study has shown that male ArKO mice develop glucose intolerance and insulin resistance that can be reversed by E2 treatment [17]. Interestingly, male humans that lack aromatase also have high insulin levels [18].

In animals lacking ERα (ERKO) [19], hepatic insulin resistance is associated with decreased glucose uptake in skeletal muscle (SM) [20]. Despite the strong evidence from these mouse models for the role of E2 in carbohydrate metabolism, the mechanisms by which E2 modulates

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Glossary

Diabetes mellitus type 2: disease caused mainly by reduced insulin activity. It is characterized by imbalance of energy metabolism, with high levels of plasma insulin and glucose. In the long term, it might affect kidneys, eyes, nervous system and heart.
Estrogen receptors α and β: nuclear receptors that bind to E2 and modulate gene expression. They are expressed in a tissue-specific way and have distinct biological activities.
Glucose transporters (GLUTs): they are a family of proteins that enables the facilitated diffusion of glucose through the cellular membrane. They are expressed in a tissue-specific way and have a crucial role in glucose metabolism. GLUT4 is the only isoform that responds to insulin action and is expressed in skeletal muscle, and white and brown adipose tissue.
Insulin resistance: state characterized by reduced insulin action in insulin-sensitive tissues. Under this situation, glucose uptake is reduced, leading to hyperglycemia and compensatory hyperinsulinemia.
Insulin-sensitive tissues: tissues where insulin stimulates the uptake of glucose through GLUT4 (e.g. skeletal muscle and white and brown adipose tissue).
Nuclear receptors: proteins located mainly in the nucleus of the cell. When activated, they interact with the promoter region of target genes, modulating protein expression.

glycemia are still not fully understood and further research is needed. As discussed below, we currently believe that ERs have an important role in this modulation.

Insulin and glucose uptake

Insulin is produced by pancreatic β cells and is extremely important for energy balance, regulating carbohydrate, protein and fat metabolism in SM, white adipose tissue (WAT) and liver, and is the most important hormone involved in maintenance of adequate glycemia [21]. In SM and WAT, insulin stimulates glucose uptake by inducing expression of a protein called glucose transporter 4 (GLUT4) [22]. GLUT4 belongs to a family of glucose transporters (GLUTs) composed of at least 12 members [23], and is the only isoform that responds to insulin. It is expressed predominantly in SM and WAT where it constitutes the rate-limiting step in insulin-induced glucose uptake. In these two tissues, insulin causes at least a twofold increase in glucose transport [22]. Because in mammals SM represents >55% of total body weight [24], the uptake of glucose into muscle cells is a rate-limiting step in the whole-body glucose metabolism and is responsible for 75% of the whole-body glucose uptake [3].

During the post-prandial phase, when plasma glucose level is high, increased insulin secretion controls glycemia. The binding of insulin to insulin receptors on the cell surface is the first step in the increased uptake of glucose into the cell. Insulin receptors are composed of two α subunits and two β subunits. The α subunits are located on the cell surface and contain the binding site for insulin, whereas the transmembrane β subunits are responsible for signal transduction. When insulin interacts with the external α subunit, autophosphorylation of the β subunit occurs at multiple tyrosines, and this results in activation of insulin signal transduction [25]. The outcome of this phosphorylation cascade is the translocation of vesicles that contain GLUT4 to the cell membrane [26]. Under basal conditions, most of the GLUT4 is localized on intracellular vesicles and only little is on the membrane. When insulin levels increase, most of the cytoplasmic vesicles migrate to the cell periphery. Once anchored to the cell membrane, GLUT4 forms a tridimensional structure that enables the facilitated diffusion of glucose from the outside into the cell [22]. Any alteration in these mechanisms – insulin signal transduction, GLUT4 expression and/or translocation to the cell membrane – can result in insulin resistance (Figure 1).

In the liver, glucose homeostasis is not dependent on GLUT4, and insulin modulates carbohydrate metabolism through direct effects on enzymatic activities. Glucose uptake is mainly maintained by the activation of glycogen synthase and glycogen phosphorylase, leading to the storage of glucose as glycogen in the liver. Additionally, insulin stimulates glycolysis through the activation of several enzymes, such as glucokinase, phosphofructokinase, pyruvate kinase and pyruvate dehydrogenase. The net result is decreased glucose output and increased glucose uptake by the liver. Abnormalities of these enzyme activities in the liver can lead to insulin resistance [20].

Estradiol and glucose transporters

GLUTs are present in almost every tissue of the human body and are crucial components in the regulation of glucose metabolism. In the late 1990s, a role for E2 in regulating GLUTs was shown. In ovariectomized rats, the amount of GLUT1 protein in the blood–brain barrier increased after E2 treatment [27] and, in the uterus, E2 treatment caused a fourfold increase in GLUT1 protein content and also increased glucose uptake [28]. In 2001, another study addressed the expression of GLUT1, GLUT3

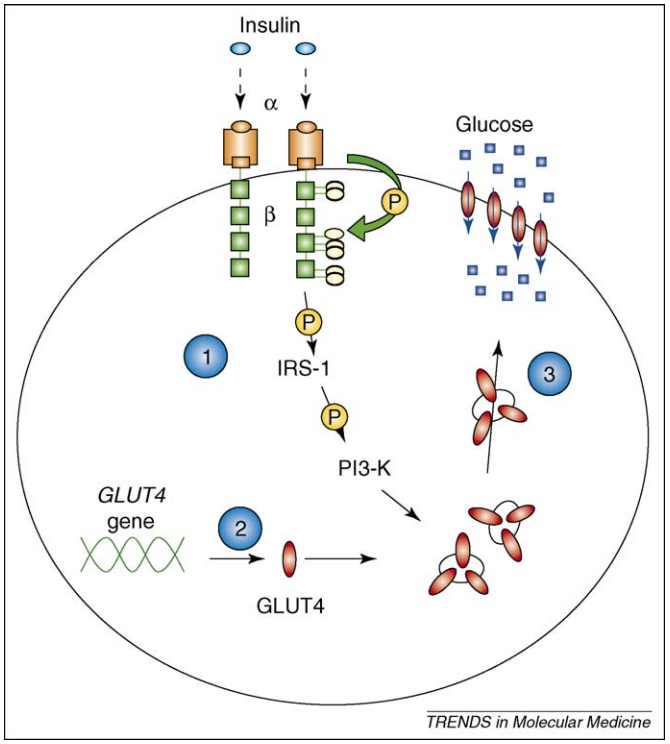

Figure 1. Model summarizing the interaction of insulin and glucose uptake in insulin-sensitive tissues. Insulin receptors are located on the cell membrane and their activation by the hormone causes the phosphorylation of the transmembrane subunit β. Once activated, several cytoplasmatic proteins are phosphorylated, including IRS-1 and PI3-K, which are essential for insulin signaling. The end result of this phosphorylation cascade is the translocation of vesicles that contain GLUT4 to the cell membrane, where the protein anchors and enables the uptake of glucose by facilitated diffusion. Any alteration in insulin signaling (1), GLUT4 expression (2), translocation or anchorage (3) causes insulin resistance. Abbreviations: GLUT4, glucose transporter 4; IRS-1, insulin receptor substrate 1; P, phosphate; PI3-K, phosphatidylinositol 3-kinase.

and GLUT4 in the frontal cortex of castrated female monkeys. It was observed that E2 treatment increased GLUT1 and GLUT4 expression in the frontal cortex, and GLUT1 mRNA content by 70% in the cortical parenchyma [29].

To understand the relationship between E2 and insulin resistance further, some studies have evaluated GLUT4 in insulin-sensitive tissues (e.g. WAT and SM) during normal gestation, gestational diabetes mellitus and PCOS. Garvey *et al.* [30] observed that in SM of patients with gestational diabetes GLUT4 content was normal when compared with those with a normal pregnancy. The authors suggested that insulin resistance in this tissue might be related to defective GLUT4 translocation. Later, the same group reported that, in adipose tissue of patients with gestational diabetes mellitus, not only the GLUT4 content was decreased but also its subcellular distribution was abnormal [31]. In 1995, Okuno *et al.* [32] showed that the GLUT4 content in adipose tissue of pregnant women was significantly lower than that in non-pregnant women, and this difference was more profound in women with gestational diabetes mellitus. In PCOS, a disease characterized by overproduction of ovarian steroids such as estradiol and testosterone, insulin-stimulated glucose uptake is reduced due to decreased amount of GLUT4 on adipocyte membranes [33].

In 2000, Sugaya *et al.* [34] evaluated the expression of GLUT4 in SM and WAT of ovariectomized rats that have been treated with E2 and progesterone (P) for 15 days. They observed that high doses of E2 and the combination of E2 and P decreased GLUT4 expression in adipose tissue. Later, another study showed that physiological doses of E2 and P reduced GLUT4 expression in SM and WAT of ovariectomized rats [35]. However, this reduction might also be attributed to reduced physical activity in these animals and not exclusively to the administered hormones. Although all these studies showed that E2 participates in GLUT4 expression and translocation, the mechanism through which the hormone regulates GLUT4 remained unclear. More-recent findings on the mechanism of E2 action, including the discovery of a second estrogen receptor, ERβ, and the possibilities of rapid non-genomic effects of estrogen inspired new investigations into the role of E2 in glucose homeostasis.

Mechanisms of estrogen action

To speculate how E2 might modulate glucose metabolism, it is necessary to understand the mechanisms through which E2 exerts its effects.

In 1962, Jensen and Jacobsen identified an estrogen-binding protein from the rat uterus and hypothesized that E2 action was mediated by this ER [5]. All actions of E2 were ascribed to this receptor. More than two decades later, ER cDNA was cloned [36,37]. In 1996, another isoform of ER was discovered. It was named ERβ [38] and the former ER is now called ERα. These two isoforms are the products of two distinct genes. In humans, ERα is located on chromosome 6 [39] and ERβ on chromosome 14 [40].

ERs belong to the steroid–thyroid hormone nuclear receptor supergene family [7]. Upon binding to E2, ERs are activated and act as transcriptional modulators by binding to specific sequences (estrogen response elements, EREs) in the promoter region of target genes [41,42]. ERα is mainly expressed in the uterus, vagina, ovaries, oviduct, pituitary and mammary glands, which are sites of classical E2 actions, but is also present in the hypothalamus, brain, bone, liver and cardiovascular system [43]. ERβ is much more widely distributed throughout the body than ERα. So far, ERβ has been shown to be the dominant isoform in the prostate, salivary glands, testis, ovary, vascular endothelium, smooth muscle, immune system and certain neurons of the central and peripheral nervous system. In these tissues, E2 action is mediated by ERβ [44]. Some tissues, such as mammary glands, bone, uterus and cardiovascular system, express both ER isoforms, with the predominance of one or the other isoform [7,44].

The presence of ERα mRNA and protein and ERβ mRNA was confirmed in adipocytes from subcutaneous and intra-abdominal fat, with clear predominance of ERα [45]. In SM, the presence of ERβ was confirmed in human vastus lateralis muscle [46] and, in mice, both ERα and ERβ have been detected in the gastrocnemius muscle [47].

Because of the great variation in ER tissue distribution and isoform predominance, the role of the two receptors has been a source of intense debate among endocrinologists, but it is now accepted that ERα and ERβ have distinct biological functions.

One of the first studies to address the differential actions of ERα and ERβ was done on neuroblastoma cells transfected with either ERα or ERβ. It was shown that activation of ERα caused an increase in length and number of neurites, whereas ERβ activation only caused neurite elongation [48]. With the development of selective agonists for ERα or ERβ, researchers could address the issue more specifically. For example, in HC11 immortalized cells, which are positive for both ERα and ERβ, obtained from pregnant mouse mammary glands, it has been observed that selective agonists for ERα cause cell proliferation and agonists for ERβ inhibit cell growth [49].

An important tool for understanding the individual actions of the two estrogen receptors and estrogen itself was the development of three knockout mouse lines, $ERα^{-/-}$, $ERβ^{-/-}$ [50] and ArKO. The evaluation of these knockout mice provided precious knowledge on the role of ERs *in vivo* and, since then, several studies have demonstrated that ERα and ERβ have distinct and sometimes opposite effects. One of the most striking examples is the development of distinct autoimmune diseases in different knockout mice. Autoimmune nephritis was diagnosed in $ERα^{-/-}$ mice [51], myeloid leukemia in $ERβ^{-/-}$ mice [52] and Sjögreńs syndrome in ArKO mice [53], showing that ERα and ERβ have specific functions in the maintenance of the normal immune system. Diverse functioning of these receptors has also been reported in several other tissues such as the uterus, breast, prostate, cardiovascular system, lung and colon [44,54–56] (Table 1).

In addition to the specific function of each receptor, interplay between these two isoforms has been reported when they are coexpressed. *In vitro* studies have confirmed that ERα and ERβ can form heterodimers that interact at EREs. Under several circumstances, ERβ opposes ERα-mediated activity and, in many systems, ERα and ERβ elicit

Table 1. Some known functions of ERα and ERβ

Site of action	Refs
Immune system	
ERα acts mainly on the spleen and thymus, and loss of function leads to glomerulonephritis. ERβ acts on the bone marrow, regulating proliferation of the progenitor cells. ERβ inactivation leads to myeloproliferative diseases in mice.	[44,56]
CNS	
In monkeys, ERβ action enhances serotoninergic transmission in the dorsal raphe, improving mood. In ERβ$^{-/-}$ mice, neuronal degeneration is increased in the substantia nigra.	[44]
Prostate	
ERβ has anti-proliferative and pro-differentiative effects in the epithelium of the mouse ventral prostate. Loss of function causes epithelial hyperplasia, increased proliferation, decreased apoptosis and failure to differentiate terminally.	[44,56]
Lung	
ERβ is important for the maintenance of the appropriate composition of the extracellular matrix. Loss of ERβ function leads to systemic hypoxia in mice.	[54]
Colon	
ERβ has an important role in the maintenance of organization and architecture of colonic epithelium. Loss of ERβ function is correlated with hyperproliferation, decreased differentiation and apoptosis in mice.	[55]
Uterus	
In the mature uterus, ERβ is involved in cervical ripening and decidualization, in parturition and implantation. ERβ is also believed to be involved in endometriosis, urinary incontinence and uterine prolapsis.	[44]
Breast	
ERα is essential for ductal growth and proliferation, whereas ERβ has anti-proliferative and pro-differentiative functions.	[44]
Glucose homeostasis	
Mice that lack ERα have hepatic insulin resistance, decreased GLUT4 uptake and expression in skeletal muscle.	[20,47,63]

opposite responses in the presence of E2 [42,57–59]. One *in vivo* example of this regulation is observed in the microarray analysis of mouse bone [60]. E2 has a key role in the homeostasis of the skeleton. In ERβ$^{-/-}$ mice, ERα-mediated gene expression was increased by 85% compared with animals expressing both receptors, supporting the idea of a 'Yin–Yang' relationship between the two isoforms [60].

Understanding E2 mechanisms of action became even more complex when it was found that ERα and ERβ could modulate gene expression without directly binding to DNA [61–63]. In these cases, ERs interact with transcription factors, which themselves directly bind to DNA, and this interaction with ER can result in either stimulation or inhibition in gene transcription [7]. Among these ER-interacting proteins are specificity protein 1 (SP1), activating protein-1 (AP-1) and nuclear factor-κB (NF-κB). It is known that these transcription factors have response elements in the promoter region of some genes and are an important part of estrogen signaling [61–63].

Thus, E2 action depends on several factors, including: (i) which receptor is present in the tissue (e.g. ERα, ERβ or both); (ii) whether the two receptors are coexpressed in cells; (iii) ERβ modulation of ERα-mediated gene expression; (iv) the interaction of ERs and transcription factors and; (v) the presence of coactivators and corepressors.

GLUT4 modulation by ERα and ERβ

The most definitive evidence that glucose homeostasis is modulated by ERα and ERβ came from studies evaluating the phenotype of ERα$^{-/-}$ mice [64,65]. Mice that lack ERα have insulin resistance, impaired glucose tolerance, adipocyte hyperplasia and hypertrophy, affecting both males and females, highlighting the importance of the E2–ERα action for the maintenance of normal glucose homeostasis in both sexes [64]. In contrast, the participation of ERβ in this homeostasis has not been clear. Ovariectomy of ERα$^{-/-}$ mice (i.e. removal of the action of E2–ERβ) improved glucose and insulin metabolism [65], indicating that ERβ activation might have a diabetogenic effect and that this might be a case where ERβ opposes the action of ERα.

In humans, there are few documented cases of ER mutations but, in 1994, a male patient with both ERα alleles inactive was described. This patient presented with severe osteoporosis, glucose intolerance, hyperinsulinemia and resistance to E2 [66], and provided evidence for the role of E2 in males but also for the importance of E2 in glucose homeostasis.

The majority of studies evaluating E2 effects on GLUT4 expression or subcellular location were done in WAT. Until recently, there was no information on the modulation of GLUT4 expression by ERα and ERβ in SM. In 2006, we have reported that ERα and ERβ modulate GLUT4 expression in SM of mice [47]. Initially, we confirmed the presence of both receptors in the gastrocnemius muscle and showed that the two receptors were colocalized in the nuclei of some cells. This colocalization has important implications for E2 activity because, if ERα and ERβ have opposite actions, cells that express both receptors might respond to E2 in different ways depending on the ratio of ERα to ERβ [49]. This means that E2 would not necessarily modulate glucose homeostasis unless the ratio of ERα to ERβ was altered. We have demonstrated that in ERβ$^{-/-}$ mice GLUT4 expression is normal, indicating the importance of ERα for the expression of this protein [47]. In ERα$^{-/-}$ mice, in which there is unopposed ERβ action, GLUT4 expression is almost absent, suggesting a repressive role of ERβ on GLUT4 expression. This low expression of GLUT4 in muscle tissue might be the cause of DM that is observed in ERα$^{-/-}$ mice. To confirm this dual modulation of GLUT4 by E2, we have shown that in ArKO mice, in which there is no E2, administration of the ERβ agonist 2,3-bis(4-hydroxyphenyl)propionitrile (DPN) blunted GLUT4 expression [47]. We hypothesize that repression of ERβ expression or action might change the balance between ERα and ERβ in cells co-expressing both receptors, thus increasing GLUT4 expression and improving glucose homeostasis in SM.

We have also evaluated some aspects of GLUT4 anchorage to the cell membrane because inappropriate protein attachment might lead to decreased glucose uptake in muscle cells. In adipocytes, one of the limiting steps in glucose uptake is the colocalization of GLUT4 and caveolin-1 in structures called caveolae [67]. In SM, the requirement for GLUT4 expression in caveolae had not been investigated. We have observed that in ERβ$^{-/-}$ mice there is decreased expression of caveolin-1 protein and no colocalization of GLUT4 and caveolin-1. However, no abnormalities in glucose uptake in SM of ERβ$^{-/-}$ mice have been reported. If it is normal, it can be concluded that colocalization is not a requirement for regular uptake of glucose in SM, in contrast to what happens in WAT.

Modulation of GLUT4 expression by selective ERα and/or ERβ modulators

Since the discovery of ERβ, researchers and pharmaceutical companies have made a great effort to develop tissue-selective ER modulators (SERMs). The idea of selectively modulating ERα and ERβ in a tissue-specific way might make it possible to replace E2 with new drugs without its unwanted side effects and also to treat various E2-related diseases.

Our working hypothesis is that imbalance of ERα to ERβ ratio, leading to over-activity of ERβ, might down-regulate GLUT4 and cause insulin resistance in SM. SERMs might help to re-establish appropriate glucose homeostasis in SM by two mechanisms: (i) ERα agonism or ERβ antagonism and (ii) modulation of the interaction between ERα or ERβ and transcription factors related to GLUT4 expression (Figure 2).

It has, for example, already been shown that androgens, which are potent modulators of muscle physiology, can decrease ERβ expression levels [68], and that low levels of testosterone in hypogonadal patients are associated with insulin resistance and DM [69]. We can speculate that in this situation low levels of testosterone might lead to elevated ERβ expression in SM and, consequently, down-regulation of GLUT4. Drugs that can inhibit ERβ action in SM should be investigated as an alternative coadjuvant therapy for insulin resistance in this tissue. Tetrahydrochrysene (*R,R*-THC), for example, is an ERβ antagonist and ERα agonist drug [70] that might be useful for GLUT4 modulation in SM because unopposed ERα action would maintain appropriate GLUT4 expression. Another possibility would be the repression of ERβcx, a splice variant of ERβ that opposes ERα action [7]. However, no ERβcx antagonist has yet been reported, and the physiological function of this ERβ splice variant is still under investigation.

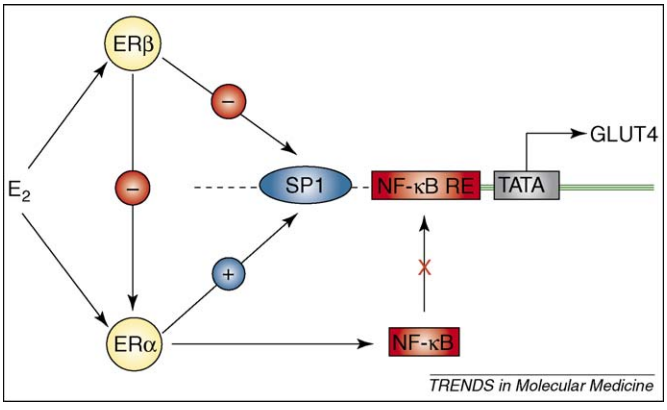

Figure 2. Model representing mechanisms by which ERα and ERβ might modulate expression of the gene that encodes GLUT4. E2 exerts its action through ERα and ERβ, which interact with the promoter region of the gene through transcriptional factors SP1 and NF-κB. The activation of ERα increases protein expression through SP1, a stimulator of GLUT4 expression. ERα also inhibits the binding of NF-κB to its response element. NF-κB is a potent repressor of GLUT4 expression and this inhibition might lead to increased GLUT4 expression. In contrast, activation of ERβ opposes ERα action and inhibits SP1-induced gene expression, reducing GLUT4 content. Abbreviations: ERα, estrogen receptor α; ERβ, estrogen receptor β; GLUT4, glucose transporter 4; NF-κB, nuclear factor-κB; NF-κB -RE, nuclear factor κB response element; SP1, specificity protein 1; TATA box, initiation site of transcription.

During recent years, several transcription factors that modulate GLUT4 expression have been shown to interact with ERs, opening several possibilities to regulate the expression of the gene that encodes GLUT4. Among these transcription factors are SP1 and NF-κB. In 1990, it was shown that the gene that encodes GLUT4 has four binding sites for SP1 in its promoter region and that SP1 increases GLUT4 expression [71]. Later, it was demonstrated that ERα and ERβ can modulate the expression of the gene that encodes GLUT4 through SP1 protein. However, the net result of ERs–SP1 action on gene expression seems to be variable and gene specific [72,73]. We speculate, based on our results in SM [47], that ERα increases GLUT4 expression through SP1, whereas ERβ does the opposite.

GLUT4 also has in its promoter region binding sites for NF-κB [74]. It is known that this transcription factor is a potent repressor of the expression of the gene that encodes GLUT4 [75] and is involved in insulin-induced regulation of GLUT4 [76]. NF-κB can interact with ERα and, as a result, NF-κB does not bind to the promoter region of some genes, such as interleukin-6, leading to a decrease in its expression [7]. We hypothesize that, when ERα is bound to NF-κB, GLUT4 expression is not repressed by this transcription factor, increasing the amount of GLUT4. Thus, ERα–NF-κB interaction in SM should also be investigated as a possible GLUT4 modulator.

In conclusion, a full understanding of modulation of GLUT4 by ERs and development of drugs that can selectively change the ERα to ERβ expression ratio or actions in tissues involved in glucose homeostasis might lead to new adjuvant therapies for DM. Although the present knowledge in not enough to indicate whether this modulation would result in improved glucose uptake and homeostasis in humans, the discovery of ERβ and its participation in the regulation of GLUT4 expression open up a new horizon for studies of glucose homeostasis and related diseases.

Concluding remarks

The identification of E2 as an important regulator of glucose homeostasis and the discovery of ERα and ERβ as modulators of GLUT4 expression in SM have created new possibilities for the development of coadjuvant therapies for DM. The idea of selectively activating ERα and repressing ERβ and, thus, increasing GLUT4 expression and glucose uptake in this tissue seems very promising. Additionally, this would prevent the development of unwanted side effects that are commonly observed with

other drugs. However, the development of drugs with such a precise tissue-specific activity has not been achieved yet. Also, the outcome of GLUT4 modulation by ERα and ERβ in SM of human patients remains unknown and further research is needed.

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Conflict of interest

J-A. Gustafsson is cofounder, deputy board member, consultant and shareholder of KaroBio AB.

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