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Estrogen receptors: new players in diabetes mellitus

Rodrigo P.A. Barros[1,2], Ubiratan Fabres Machado[2] and Jan-Åke Gustafsson[1]

[1] Department of Biosciences and Nutrition, Karolinska Institute, S-141 86 Novum, Sweden
[2] Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, Avenida Professor Lineu Prestes, 1524, 05508-900, São Paulo, SP, Brazil

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

Corresponding author: Gustafsson, J-Å. (Jan-Åke.Gustafsson@mednut.ki.se).
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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

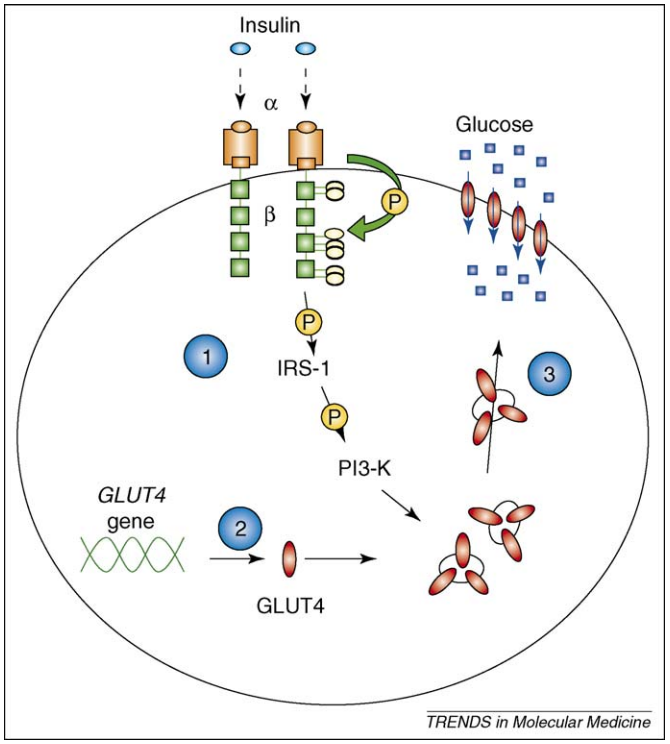

Figure 1. Model summarizing the interaction of insulin and glucose uptake in insulin-sensitive tissues. Insulin receptors are located on the cell membrane and their activation by the hormone causes the phosphorylation of the transmembrane subunit β. Once activated, several cytoplasmatic proteins are 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.