Review

MOLECULAR METABOLISM

The impact of ERα action on muscle metabolism and insulin sensitivity — Strong enough for a man, made for a woman

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ABSTRACT

Background: The incidence of chronic disease is elevated in women after menopause. Natural variation in muscle expression of the estrogen receptor (ER)α is inversely associated with plasma insulin and adiposity. Moreover, reduced muscle ERα expression levels are observed in women and animals presenting clinical features of the metabolic syndrome (MetSyn). Considering that metabolic dysfunction elevates chronic disease risk, including type 2 diabetes, heart disease, and certain cancers, treatment strategies to combat metabolic dysfunction and associated pathologies are desperately needed.

Scope of the review: This review will provide evidence supporting a critical and protective role for skeletal muscle ERα in the regulation of metabolic homeostasis and insulin sensitivity and propose novel ERα targets involved in the maintenance of metabolic health.

Major conclusions: Studies identifying ERα-regulated pathways essential for disease prevention will lay the important foundation for the rational design of novel therapeutics to improve the metabolic health of women while limiting secondary complications that have plagued traditional hormone replacement interventions.

Keywords Estrogen action; Estrogen receptors; Insulin sensitivity; Metabolic homeostasis

1. INTRODUCTION

For over two decades researchers have shown strong relationships between estrogen action and metabolic health in women. Moreover, epidemiological reports indicate that chronic disease incidence increases in women following menopause. Considering that menopause occurs on average at age 51 (National Institutes of Health, NIA www.nia.nih.gov) and that life expectancy has increased for white females to ~80.6 years (The National Vital Statistics Report, 2012), women in the modern era are challenged with heightened disease risk associated with increasing adiposity and metabolic dysfunction for up to three decades of life. Although many researchers and clinicians have focused on the impact of replacement estrogens to ameliorate clinical symptoms and provide protective health benefit, an incomplete understanding of hormone action as well as estrogen receptor distribution and function has contributed to our continued confusion and failure to advance therapeutic strategies to combat chronic disease-associated pathologies for women.

Regarding the benefits of exogenous hormone replacement therapy (HRT) on diabetes risk after menopause, large randomized clinical trials of postmenopausal estrogen-based HRT compared with placebo as well as prospective cohort studies, have shown reductions in fasting glucose, insulin, and incidence of new onset T2D [1—6]. Meta-analyses indicate a 30% lower relative risk [RR 0.7 (CI, 0.6—0.9)] of new-onset T2DM in postmenopausal women following HRT compared with placebo [7]. The mechanism by which HRT reduces T2D incidence in postmenopausal women is not yet known however molecular studies in rodents indicate that this protective effect may be achieved in part as a consequence of estrogen-induced insulin-sensitization. Considering that 75—85% of insulin-stimulated glucose disposal is into skeletal muscle and since skeletal muscle typically represents 30—40% of total body mass, we have focused our efforts in understanding the effects of estradiol/ERα action in this tissue.

In this review, we will present studies related to the biological actions of estrogen receptors in skeletal muscle in controlling glucose homeostasis and insulin sensitivity, as insulin resistance and metabolic dysfunction are identified as major underpinnings involved in the pathobiology of chronic diseases that plague our society today. We will present basic research suggesting that the estrogen receptor (ER) α form ERα (encoded by the gene *ESR1*) is an important target to combat metabolic dysfunction.

2. MOLECULAR MECHANISMS OF ESTROGEN RECEPTOR (ER) ACTION

Identification and phylogenetic analysis of steroid receptors in basal vertebrates and reconstruction of the sequences and functional attributes of ancestral proteins led to the conclusion that the first steroid

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receptor was an estrogen receptor [8]. Early studies in reproductive tissues investigating the actions of estradiol led to the paradigm of classical nuclear ERs as ligand-activated transcription factors [9]. Although ERs exist in two main forms, α and β, which have multiple splice variants of unknown function, ERs exhibit tissue specificity in expression and function [10]. The classical, or genomic mechanism of ER action, describes a scenario whereby the ligand-activated ER dissociates from its chaperone and binds as a dimer either directly to estrogen response elements (ERE) in target genes promoters or indirectly to AP-1 or SP-1 response elements through protein tethering association with other transcription factors to DNA [11] (Figure 1). ERs recognize DNA sequences, EREs, which have a 13-base pair consensus sequence (GGTCAnnnTGACC) [12]. The binding of an ER dimer to an inverted palindrome indicates that the two monomers are arranged in symmetrical face-to-face configuration. Following DNA binding, ER dimers interact with basal transcription factors leading to activation or repression of target gene expression. Overlap in binding sites for E_2-liganded ERα and ERβ is observed when receptors are expressed individually; however, when both ERs are present, few sites are shared. Each ER restricts the binding site occupancy of the other, with ERα typically dominating [13]. Moreover, ligand-activated ERs promote transcription in a cyclic fashion. The repeated cycling of the receptor complex on and off target promoters in the presence of continuous E_2 stimulation may represent a mechanism of continuous sensing and adaptation to the external hormonal milieu to yield the appropriate transcriptional response [14].

In addition to classical signaling, E_2-ERα can act within seconds to minutes via extranuclear and membrane-associated forms of the receptor [15] (Figure 1). Membrane associated receptors localize to caveolae where they congregate with other signaling molecules, including G proteins, growth factor receptors, tyrosine kinases (Src), linker proteins (MNAR), and orphan G-protein coupled receptors (GPCRs) [16]. In a variety of cell types, membrane and extranuclear pools of ERs activate protein kinases that phosphorylate transcription factors to promote their nuclear translocation and transcriptional action [15,17]. The G protein-coupled estrogen receptor (GPER), or GPR30, has been reported to respond to E_2; however, its role as an ER is still controversial. Although emerging evidence in murine muscle cells shows diverse distribution of GPR30 in the nucleus, mitochondria, and cytoplasm [18], functional aspects of this receptor *in vivo* remain unclear; thus, GPR30 will not be discussed in this review.

With respect to ER action of reproductive function, the current thinking is that reproductive effects are almost exclusively mediated via classical nuclear ERs acting as ligand-activated transcription factors. However the role of nuclear vs. extranuclear actions of ERα in the regulation of metabolism and insulin action remains controversial and inadequately interrogated [19]. More recently, an emerging theme in the field is that for many targets, nuclear and non-nuclear signaling must collaborate to achieve the full biological action of estradiol [20]. Although non-genomic signaling is supported for specific cell types under defined conditions, scientific dissection of these pathways remains challenging, thus a central question in the field pertaining to the tissue-specific sites of action and the molecular mechanisms by which ERα selectively activates or represses target genes remains.

2.1. Estrogen action, metabolic function, and insulin sensitivity

Reduced whole body ERα expression or impaired ERα function due to genetic alteration (including genetic variants) has been linked with increased prevalence of specific features of the metabolic syndrome including insulin resistance and obesity in both male and female human subjects and rodents [21–28]. Since obesity is a prominent phenotype observed in estrogen or ERα deficient rodent models, the specific role of ERα in adipocytes and the phenotypic outcomes of obesity as a consequence of adipose-specific ERα deletion in mice is currently under investigation by several laboratories around the world. Whether the obesity phenotype observed in whole body $Esr1^{-/-}$ mice or women harboring an *ESR1* polymorphisms is explained by impaired ERα action in adipose tissue specifically or as a secondary phenotype of ERα impairment in other metabolic tissues requires resolution.

Insulin resistance is a central disorder in the pathogenesis of obesity and type 2 diabetes and is a defining feature of the Metabolic Syndrome, a clustering of metabolic abnormalities including obesity, hypertension, glucose intolerance, and dyslipidemia [29,30]. Metabolic dysfunction and a clustering of these abnormalities is worrisome as

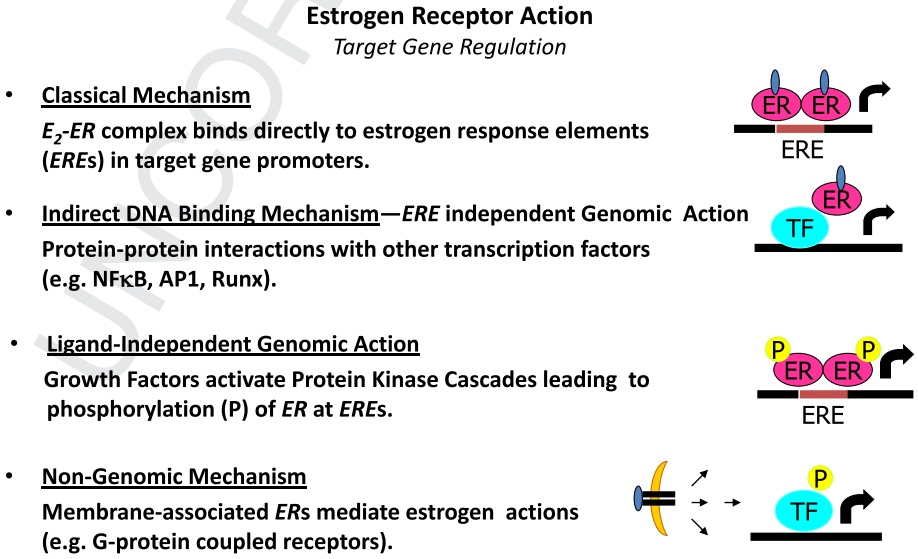

Figure 1: Molecular actions of ERα to activate or repress target genes by classical DNA binding, non ERE genomic action, or non-genomic actions. ERE, Estrogen response element in target gene promoters; P, phosphorylation; TF, transcription factor.

