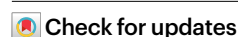


Metabolic Messengers: oestradiol

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Oestradiol (E2), a steroid hormone derived from cholesterol, has long been recognized for its central role in female reproduction and pathobiology of menopause. However, accumulating evidence underscores a critical role for E2 in the regulation of systemic metabolism in both women and men. The metabolic actions of E2 are predominantly mediated by oestrogen receptor α (encoded by *ESR1*), a nuclear receptor with heritable expression patterns and tissue-specific transcript levels highly correlated with indices of metabolic health in both sexes. Here we provide an overview of the cell-specific actions of E2 and its receptors (α and β) in modulating key metabolic pathways. We contextualize these mechanistic preclinical studies with epidemiological data linking the menopausal transition to a marked rise of metabolic disease risk and provide evidence that E2 replacement mitigates this risk by preserving metabolic health.

Oestrogens are a class of steroid hormones predominantly produced by granulosa cells in ovary of females and include oestrone (E1), oestrinol (E3) and most notably oestradiol (E2), in highest concentrations in reproductive females. Although oestrogens circulate at much lower concentrations in men compared with women, oestradiol in particular, which is predominantly produced by the aromatization of testosterone in males, is shown to be critical for the maintenance of metabolic health in male rodents and men^{1–3}. Aromatization of androgens to oestrogens is not limited to reproductive organs, but also occurs in extragonadal tissues, including adipose tissue and the central nervous system (CNS)^{4–7}. However, extragonadal oestrogen production on tissue and systemic metabolism remains inadequately understood. Aromatization by the enzyme aromatase (*CYP19*) involves enzymatic alteration of androstenedione and testosterone, to yield E1 and E2, respectively, and E2 has the highest receptor binding affinity and is more effective at inducing oestrogenic activation of target genes than E1 or E3 (refs. 8,9). This explains the clinical focus of E2 for human health. Oestrogens produce biological action predominantly via receptor-mediated processes acting on gene transcription in the nucleus; however, nongenomic signalling also occurs within the cytosol as well as plasma and organelle membranes leading to rapid changes in metabolism, although, these pathways are less-well understood.

Preclinical models of oestrogen insufficiency or modulation of oestrogen receptor (ER) expression have been instrumental in revealing

cell, tissue and sex-specific actions of oestrogens. Although oestrogens were discovered in the 1930s–1940s (Fig. 1), and the two primary forms of the ER were the first of the nuclear receptor superfamily to be cloned (1980s–1990s), inadequate understanding of oestradiol production (endocrine versus paracrine/autocrine action), the cell-specific actions of oestradiol, including identification of target genes (activated and repressed), as well as nongenomic signalling via receptor-mediated and receptor-independent pathways, have hindered advancement of clinical care, especially for women.

The maintenance of ovarian hormone production is linked with morbidity and mortality, considering that interval length between menarche and menopause is positively associated with longevity and a reduced odds ratio of cardiometabolic disease^{10,11}. In menopausal women, there is a shift to extraovarian production of oestradiol, which circulates at markedly reduced levels. A reduction in circulating oestradiol concentration and impairment in target tissue action are thought to underlie the significant increase in metabolic disease incidence during this life phase^{12–14}. Evidence from the largest National Institutes of Health (NIH)-funded multi-site longitudinal epidemiological trial studying women across the menopausal transition (Study of Women's Health Across the Nation (SWAN); Fig. 1) shows metabolic disruptions decades before the clinical determination of menopause, the final menstrual period (FMP)¹⁵. These findings indicate that circulating oestradiol levels are a poor index

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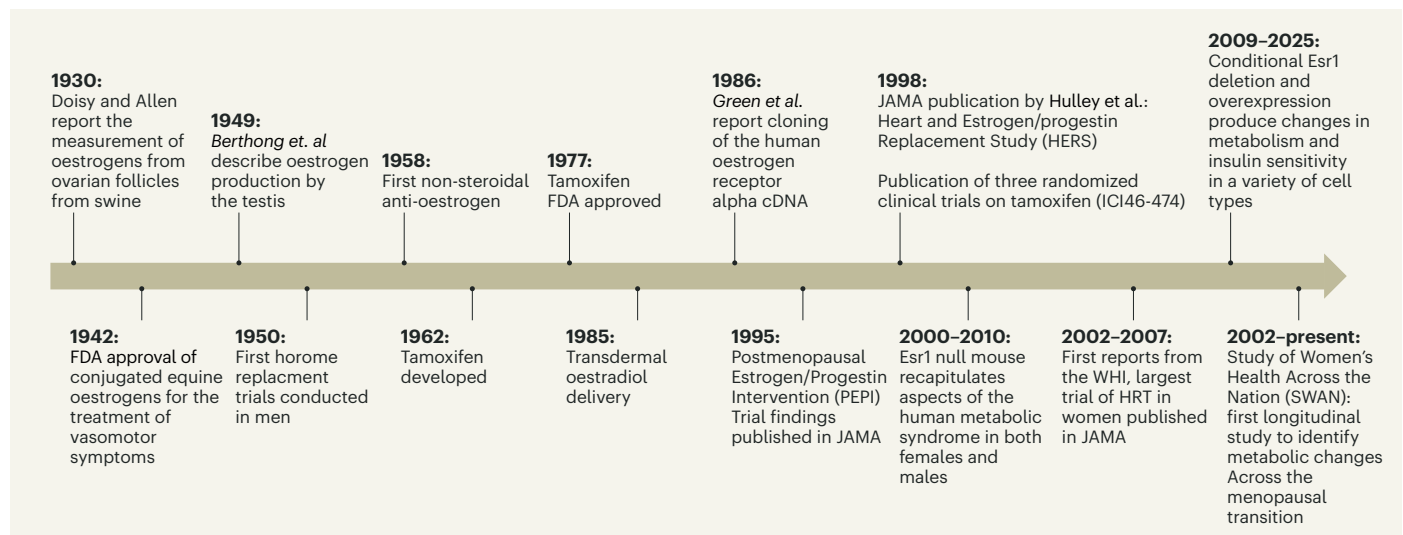


Fig. 1 | Timeline of important discoveries in oestrogen research from discovery to clinical application. Significant progress has been made over the past 75 years in the understanding of oestradiol action and the development of therapeutics that can serve to replace or diminish/antagonize the hormone and its cognate receptors. Studies from the 1930s–1960s were focused on identifying oestrogens and studying clinical phenotypes in the absence of hormone and hormone replacement. Studies from the 1960s–1990s were focused on identifying ERs and the mechanisms of oestrogen action in a limited number of cell types. In the late 1990s and early 2000s, large interventional trials (for example the NIH-

sponsored WHI) were conducted to understand the clinical efficacy of oestrogen replacement and the first studies employing mouse genetics to ablate ERs were performed. SWAN (initiated in 1994 and is ongoing), was the first NIH-sponsored multi-site, longitudinal study to report on clinical features of a multi-ethnic population across the menopausal transition. From the early 2000s to present, novel tools and techniques have been leveraged to study the molecular mechanisms of oestrogen/ER action in a tissue and cell-specific contexts utilizing bulk and spatial-focused multiomic assays and chromatin architecture analyses. HRT, hormone replacement therapy.

of oestrogen action and metabolic health; thus, a clearer understanding of ER status seems of critical clinical importance during this life phase.

To combat vasomotor symptoms associated with menopause (including hot flashes), the US Food and Drug Administration (FDA) approved hormone replacement in 1942. Hormone replacement for the indication of osteoporosis was not approved until 1988 (Fig. 1). Despite USFDA approval, interventional hormone replacement trials, including single-hormone oestradiol and conjugated equine oestrogens with progestin medroxyprogesterone acetate, were not initiated until the early 1990s¹⁶. Not until the early 2000s were reports published from the largest NIH-funded interventional trial, studying over 27,000 women between the ages of 50–79 years^{17,18}. Because participants were widely heterogeneous for time since menopause (including women 10–30 years after FMP), confusion and concern regarding the biological impact of E2 administration and disease risk (for example breast cancer) caused dramatic reductions in menopausal hormone therapy prescriptions^{19,20}. Debate over the timing of hormone administration and the impact of hormone replacement on disease risk and primary disease prevention is ongoing^{20–23}.

Discovery of oestrogens and oestrogen receptors

Measurement of oestrogens (specifically estrone) in the urine of pregnant women, was first reported in the 1930s^{5,24,25} (Fig. 1) and over the next decade, the field focused on testosterone aromatization. These seminal studies in endocrinology set in motion a century of intense investigation to understand the structure, biosynthesis, secretion patterns, sites and mechanisms of hormone responsiveness, as well as the clinical consequences of ovarian hormone action by receptor-dependent and -independent means.

A major conceptual advance in the 1970s–1990s was the observation of extragonadal expression and activity of aromatase cytochrome P450 (refs. 26–29). This research expanded the field view of oestrogen biosynthesis by extragonadal sites and resolved important questions about cell-specific oestrogens acting in an

autocrine/paracrine versus endocrine fashion. These studies were foundational for the development of aromatase inhibitors as a current standard of care for breast cancer treatment^{30,31}. Oestradiol is degraded by sulfation via sulfotransferases (13 human forms) with SULT1E1 showing the lowest K_M for estrone and oestradiol, and differential expression levels associated with sex-biased drivers of cardiometabolic disease^{32–35}. Oestrogens act within a narrow concentration range for maximal biological efficacy; thus, integration of rates of oestradiol production by ovarian and extragonadal sources with rates of degradation is critical for the maintenance of metabolic health.

Oestrogens are lipophilic and pass freely through membranes, exerting biological action predominantly by nucleocytoplasmic α and β forms of the receptor (encoded by distinct genes *ESR1* (ref. 36) and *ESR2* (ref. 37), respectively). The α form of the receptor is expressed at markedly higher levels than β and is shown to possess higher ligand affinity and downstream biological action for most metabolic cell types. ERs have six domains, A–F (Fig. 2a), each exerting unique elements of ER biology and cellular action^{38–40}. *ESR1* includes eight exons that encode a 66-kDa full-length protein (Fig. 2a)⁴¹.

Oestradiol action by genomic versus nongenomic, receptor-dependent and receptor-independent mechanisms

ESR1 receptor expression is heritable, and receptor levels are positively associated with indices of metabolic health^{42–44}. Oestradiol binding initiates a reorientation receptor conformation⁴⁵ dictating cofactor association and transcriptional activity, which modulates processes including cell differentiation, proliferation, survival and metabolism⁴⁶. In addition to direct DNA binding (Fig. 2b), ERs can tether to transcription factors via protein–protein interaction (Fig. 2c) or be activated via post-translational modification (Fig. 2d). Although it is estimated that >90% of ER abundance is localized to the nucleus, mice genetically engineered to express only cytosolic-localized receptor retain specific metabolic functionalities (Fig. 2e,f). The ligand-dependent

transcriptional activity of ER α is mediated by the activation function (AF) site located in the N-terminal A/B domain (AF1) and the C-terminal, ligand-binding domain (AF2-ligand dependent)^{47,48}.

Oestradiol can also remodel cellular membranes (for example plasma membrane, lipid rafts and outer mitochondrial membrane) by controlling cholesterol-linked fluidity^{49,50} and mitochondrial electron transport chain functionality (ATP and H₂O₂ production)⁴⁹ independent of ERs, although evidence supporting direct hormone action to improve in vivo metabolic health in the absence of ER α is lacking. An abundance of data shows that genomic actions of E2-ER α are required for the maintenance of mitochondrial function, metabolic health and insulin sensitivity^{42,51–55}. Indeed, compensatory elevation of circulating oestradiol in the global *Esr1* null mouse is inadequate to preserve mitochondrial metabolism and metabolic health, suggesting that oestradiol levels alone cannot overcome metabolic dysfunction consequent to ER α deletion/inactivation^{51,56}.

With respect to potential oestradiol-induced receptor-mediated actions in mitochondria, although there is evidence for the expression of both forms of the receptor in mitochondrial fractions of breast cancer cell lines and reproductive tissues^{57–60}, a direct role for mitochondrial-localized ERs in the regulation of metabolism and mtDNA-transcribed targets in non-neoplastic cells remains unknown. Thus, the localization of ERs in mitochondria and the contribution of nongenomic action of E2 independently on mitochondria requires additional investigation.

Physiological actions of oestradiol in metabolic tissues

Ovariectomized and *Esr1* null mice

Ovarian oestrogens play a major role in the regulation of energy homeostasis¹². Oestradiol suppression⁶¹ or decreased E2 following ovarian senescence or hysterectomy⁶²/ovariectomy (OVX)⁶³ are associated with hyperphagia and reduced energy expenditure driving adipose tissue weight gain (Fig. 3). Oestradiol replacement prevents obesity and

metabolic dysfunction by decreasing feeding and increasing energy expenditure by enhancing volitional activity and non-exercise energy expenditure⁶⁴. The effects of E2 on energy homeostasis are largely mediated by ER α , given that selective ER α agonist propylpyrazole triol displays anorectic action⁶⁵, whereas ER β agonist diarylpropionitrile causes weight gain⁶⁶. ER α deletion in male and female mice promoted hyperphagia, hypometabolism, increased adiposity (both hypertrophy and hyperplasia), hyperleptinaemia and insulin resistance^{51,67,68}. In contrast, deletion of ER β failed to promote metabolic dysfunction or obesity⁶⁹.

Next, without priority, we present the impact of oestrogen action in specific organ systems, tissues and cell types.

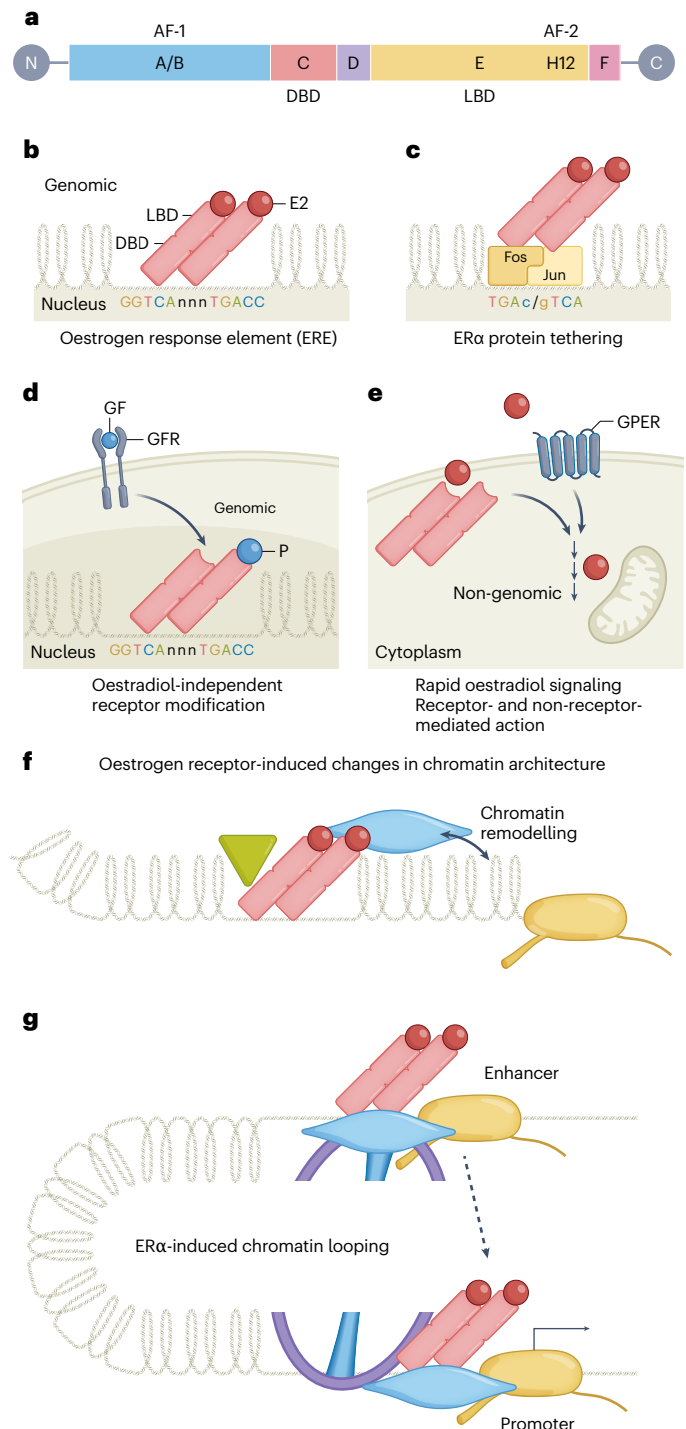


Fig. 2 | Oestrogen receptor-mediated action on metabolism. **a**, Schematic of the ER α illustrating the six domains A–F, oriented from the amino to carboxy terminus, showing the respective activation function domains, AF1 and AF2. The ligand-binding domain (LBD) binds oestradiol, which causes a conformation shift in the structure of ER α protein and a critical repositioning of helix 12 (H12) allowing for engagement of activation functions and additional recruitment of cofactors critical for specificity of ER α action. The DNA-binding domain (DBD) of ER α interacts with oestrogen response element (ERE) motifs in accessible regions of chromatin. **b**, Genomic actions of ER α includes binding of the receptor to ERE motifs in DNA. **c**, ER α can tether to other transcription factors by protein–protein interaction (for example via Fos/Jun dimer to AP-1 sites). **d**, Ligand-independent signalling can occur by rapid action of growth factors to modulate modifications of ER α , which alter downstream cytosolic signalling and possibly interactions with proteins involved in regulation of mitochondrial metabolism. **e**, Rapid oestrogen signalling in the cytoplasm achieved by receptor-dependent and -independent action on metabolic cascades, as well as mitochondrial function by inner and outer membrane alterations in fluidity, protein turnover and protein modification (for example phosphorylation and acetylation) impacting processes including energetics, calcium homeostasis, cholesterol biosynthesis and steroidogenesis. **f**, Fundamental mechanism of ER α -driven genomic action includes access to EREs of target genes by the recruitment of pioneer factors (lime triangle; for example, FOXA1 and GATA 3) that modify the chromatin state. Liganded receptor induces a unique conformation leading to the recruitment of coactivator complexes (for example SRC3 and p300), facilitating RNA Pol II translocation to the transcription start site (TSS). Unique assembly of cofactors drive increased transcription of the ER target gene. **g**, Model of chromatin looping to promote the interaction between enhancers and promoters near the gene TSS. Enhancers are characterized by the presence of enhancer RNA, Pol II, p300, acetylation of histone 3 lysine 27 (H3K27Ac) and monomethylation of histone H3 lysine 4 (H3K4Me1). Cohesin and mediator proteins promote the connection between the enhancer and promoter(s) near the TSS¹¹⁶. Figure adapted from ref. 38, Oxford University Press.

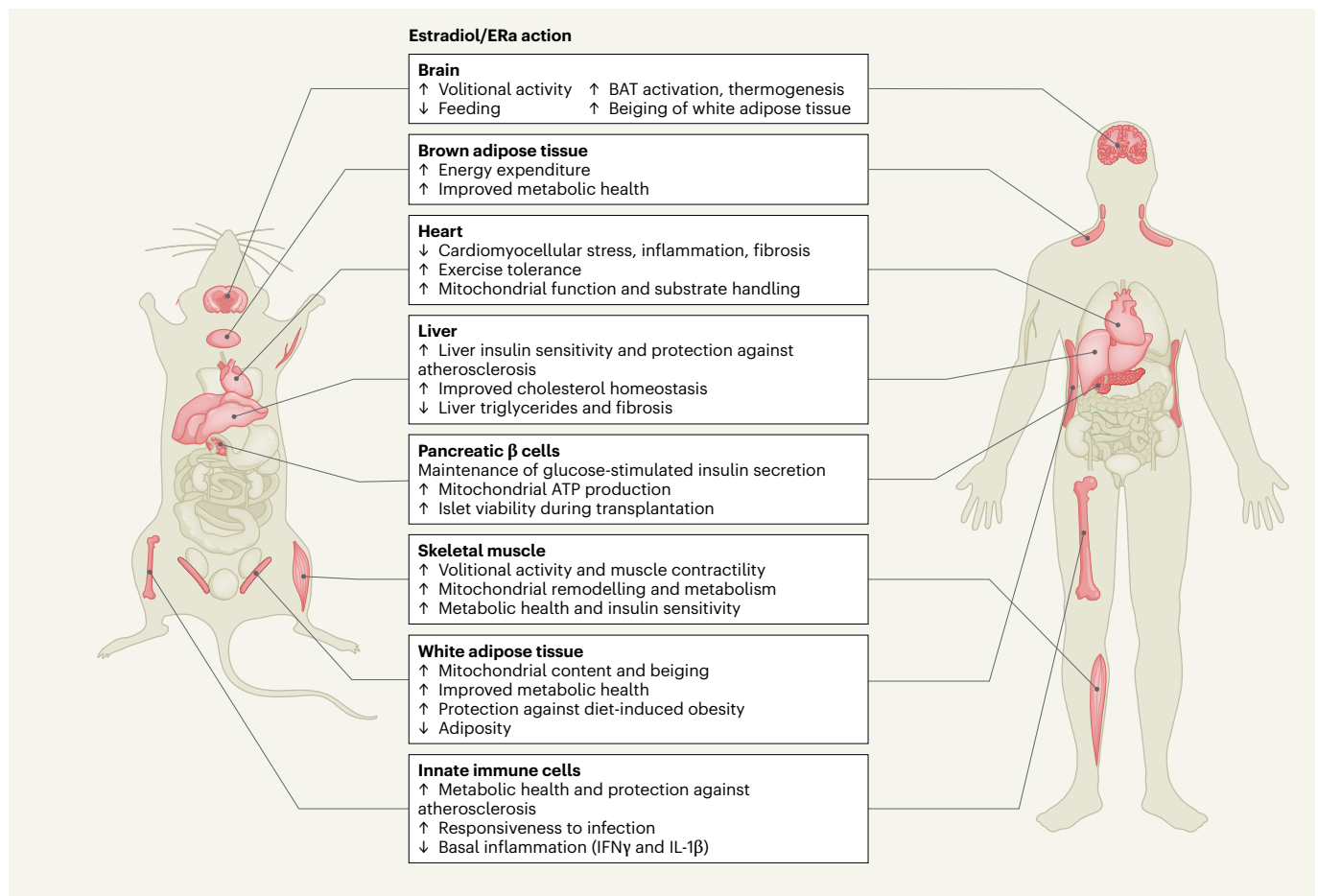


Fig. 3 | Tissue-specific regulation of metabolism by oestradiol/ER α .

ERs, specifically Esr1/ER α , are highly expressed in most metabolic tissues. Ovariectomy with oestradiol replacement, as well as LoxCre approaches in mice to manipulate *Esr1*/ER α in a tissue-specific and time dependent strategy have produced largely consistent findings between laboratories. Tissue-specific deletion of *Esr1* from brain, heart, liver, skeletal muscle, pancreatic islets, BAT, WAT and macrophages reproduce selective phenotypes of the whole body

Esr1 null mouse and phenocopy specific features of metabolic disruption and heightened metabolic disease risk observed during menopause in women. Notably, in many instances similar metabolic features are also recapitulated in male *Esr1* knockout (KO) rodents. Thus, by and large, actions of ER α are conserved between female and male rodents, and these preclinical studies are consistent with observations of oestrogen action on metabolism in humans. IL, interleukin; IFN, interferon.

Brain

Oestrogens are locally produced in a variety of brain regions⁷, and ERs are abundantly expressed in the CNS and are responsive to central administration of E2 (ref. 70). Genetic models show that central ER α is required for optimal body weight management. Compared with wild-type animals, both male and female CNS-specific ER α -null mice develop hyperphagia, visceral (but not subcutaneous) adiposity, and show decreased energy expenditure and volitional locomotor activity, as well as compensatory elevation of circulating E2 (ref. 71). Specifically, ER α is highly expressed in several hypothalamic nuclei (for example ventromedial (VMH), arcuate (ARC), paraventricular (PVH), preoptic (POA) and lateral (LHA) areas) compared with significantly lower ER β expression⁷⁰. The actions of oestrogens on food intake are thought to predominate in pro-opiomelanocortin (POMC) neurons⁷⁰, as ER α deletion from POMC-selective neurons drive hyperphagia without alteration in energy expenditure or fat distribution⁷¹. The molecular mechanisms mediating the effect of oestrogens on POMC neurons are unclear; however, recent findings indicate that E2 inhibits AMP-activated protein kinase⁷².

While the ARC is considered central for hypothalamic feeding control, the VMH seems key for modulation of energy expenditure⁷³. Electrical, pharmacological, and hormonal stimulation of this brain region increases interscapular brown adipose tissue (BAT) temperature.

Although BAT itself expresses ERs^{42,74}, classical electrophysiological data show that E2 modulates the excitability of neurons in the VMH through a cAMP-dependent mechanism mediated by steroidogenic factor-1 (SF1) neurons. In mice lacking ER α selectively in SF1 neurons, high fat-diet feeding increased body weight and visceral adiposity further above controls, but only in females⁷¹. Despite similar caloric intake between the genotypes, hypometabolism because of reduced BAT thermogenesis was explained by a reduced sympathetic outflow and diminished expression of uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor γ , PGC-1 α and β 3 adrenergic receptors. Chemogenetic activation of ER α -positive VMH neurons stimulated heat generation and movement in both sexes; however, sex-biased expression of the repressing gene seems to regulate thermogenesis in females⁷⁵. Moreover, E2 and CRISPR-mediated activation of melanocortin-4 receptor (MC4R) signalling in VMH neurons by ER α increased volitional physical activity⁷⁶. Collectively these findings show that oestrogen action in specific brain regions controls complex metabolic traits including feeding, thermoregulation and volitional activity.

Cardiac tissue

Before menopause, a female-biased protection against cardiovascular disease, including atherosclerosis and heart failure is observed⁷⁷. There is high metabolic demand for ATP production by oxidative

phosphorylation within cardiomyocytes⁷⁸. Cardiac tissue relies heavily on the metabolism of fatty acids to fuel contraction; however, in the diabetic or failing heart, there is a shift in substrate utilization to glucose and ketones⁷⁹. Positron emission tomography imaging shows that myocardial fatty acid oxidation rates are markedly higher in women compared with men, and trended higher in postmenopausal women receiving hormone replacement versus untreated⁸⁰. In the specific case of cardiac hypertrophy, findings of oestradiol acting via ER β have been shown (findings confounded by the use of global deletion models); however, recent evidence suggests a more significant role for ER α in the protection of cardiomyocytes from mitochondrial dysfunction, oxidative stress, fibrosis and cardiac hypertrophy⁸¹. Cardiomyocellular ER α is now implicated in the production of heart-derived extracellular vesicles that exert metabolic reprogramming of peripheral tissues and energy homeostasis⁸¹. As aerobic capacity is the best predictor of morbidity and mortality, and cardiac output is determinant of aerobic fitness (VO₂ max), the importance of cardiomyocellular metabolism in heart health and the role that the heart plays in orchestrating systemic metabolism^{82,83}, especially in response to oestradiol and ER signalling, requires further exploration.

Liver

ER α is significantly reduced (~50%) in the liver of humans with poorly controlled diabetes, as well as db/db mice compared with controls⁸⁴. Experimental disruption of hepatic oestrogen action in adult mice recapitulates aspects of the metabolic syndrome⁸⁵. 17 β -Oestradiol inhibits hepatic gluconeogenic genes, including phosphoenolpyruvate carboxykinase 1 (Pck-1) and glucose-6-phosphatase (G6Pase) and this effect is absent in mice lacking liver ER α (LERKO; Cre driven by the albumin promoter), which display fasting hyperglycaemia and impaired glucose tolerance^{85,86}. Liver lipids and triglyceride levels are also elevated in LERKO mice consequent to lipogenesis by induction of fatty acid synthase (Fas) and acetyl-CoA carboxylase (Acc1)^{87,88}. Reduction in basal metabolic rate for LERKO animals versus controls was paralleled by atherosclerotic lesion progression in the context of western diet feeding⁸⁸. Additionally, relevant to oestradiol action in the liver, interrogation of oral versus transdermal preparations of oestradiol, with particular focus on hepatic first-pass hormone delivery by portal vein circulation should be considered⁸⁹, and whether liver ER α can be selectively targeted in a ligand-independent manner to protect against metabolic disease, including metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatohepatitis (MASH) should be investigated.

Skeletal muscle

Numerous studies have shown that oestradiol treatment protects against muscle injury⁹⁰ and insulin resistance driven by high fat-diet feeding, inactivity or genetic obesity. Similar findings in cell culture show that oestradiol promotes muscle insulin action and fatty acid oxidation. *ESR1/Esrl* in the muscle of humans and rodents is positively associated with indices of metabolic health, including insulin sensitivity in both sexes^{52,91}. Moreover, in-depth RNA sequencing of muscle from diverse strains of mice shows strong *Esrl* heritability and significant correlations between *Esrl* expression and transcripts associated with mitochondrial remodelling and mtDNA replication. With respect to clinical relevance, *ESR1* is markedly reduced in the muscle from premenopausal women displaying clinical features of metabolic syndrome, including obesity and impaired glucose tolerance⁵². To establish a causal relationship between muscle *Esrl* expression and metabolic health, gene deletion and overexpression models have been studied over the lifespan^{52,91}. Skeletal muscle insulin resistance, glucose intolerance, increased adiposity, reduced myocellular oxidative metabolism and disrupted metabolomic profiles were consequent to skeletal muscle-selective *Esrl* deletion in both female and male animals^{52,91}.

Diminished ER α action in the muscle stalled mtDNA replication and produced morphological changes in mitochondrial inner and outer membrane structure in both female and male mice that appears consequent to mitochondrial fission incompetence^{52,92}. These mitochondrial-related alterations disrupted fatty acid metabolism, promoting a marked accumulation of lipid in muscle, and this is thought to underpin muscle inflammation and insulin resistance leading to decrements in metabolic health. Notably, impairment in muscle ER α action blunts physiological adaptations in metabolism during exercise training intervention^{52,91}. In contrast, in muscle-selective *Esrl* overexpression mice, enhanced skeletal muscle insulin sensitivity and protection against diet-induced insulin resistance was paralleled by enhanced mitochondrial fission dynamics, increased mitochondrial cristae density and heightened oxidative capacity that enhanced exercise-induced mitochondrial adaptation⁹¹. These findings suggest that skeletal muscle ER α is critical for the maintenance of mitochondrial function and insulin action, and that muscle *ESR1* may be an effective target to combat insulin resistance and diseases associated with metabolic dysfunction.

Pancreatic β -cells

Diabetes, type 1 and 2, manifests when pancreatic β -cells produce insufficient insulin to promote glucose disposal into peripheral tissues and regulate endogenous glucose production by the liver. Although diabetes type 1 and 2 yield vastly different phenotypes, preservation of β -cell mass is a key therapeutic strategy for both diseases⁹³. Considering that there is a reduced prevalence of diabetes in premenopausal women compared with age-matched men⁹³ and that female ZDF rats are protected against β -cell failure compared with males suggests that harnessing the protective effects of oestradiol/ER α may prove efficacious in the treatment or prevention of type 2 diabetes in women. Moreover, because pancreas biopsies from healthy women show a significant increase in β -cell number compared with men, there is additional evidence of a sex-biased enhancement of β -cell viability to improve islet transplantation outcomes for people with type 1 diabetes⁹⁴.

Studies in islet-specific ER α knockout (KO) mice highlight the mechanistic importance of ER α in islets/ β -cells to regulate insulin synthesis and protect against β -cell apoptosis during stress. Although the protective actions of oestrogens/ER α in pancreatic β -cells are well documented, the mechanistic underpinnings seem to reflect a complex crosstalk of genomic and rapid nongenomic signalling^{95,96}. In part, ER α prevents tissue lipid accumulation and promotes β -cell survival by maintaining mitochondrial health, and suppressing endoplasmic reticulum stress and apoptotic signalling⁵⁴. Additional research is required to understand the molecular changes that occur in β -cells during the menopausal transition and how β -cell ER α can be selectively targeted to prevent or mitigate the complications associated with diabetes.

Brown adipose tissue

Distinct from white adipose tissue (WAT), brown adipocytes are characterized by the uncoupling of mitochondrial respiration from ATP synthesis to produce heat in thermoregulation. During cold exposure, mitochondrial remodelling shifts substrate metabolism to fatty acid mobilization linked with the induction of UCP1 to produce heat. WAT browning and BAT activation are thought to contribute to improvements in metabolic homeostasis and insulin action. Females have increased BAT volume and activation, and female brown adipocytes are more highly enriched in mitochondria compared with males^{97–99}. BAT metabolism and WAT beiging are induced by E2. *Esrl* deletion from BAT impairs dynamin-related mitochondrial fission control over adipocyte fatty acid oxidation and reduced thermoregulatory and glucoregulatory capacity during cold exposure⁴².

White adipose tissue

Clustering of metabolic abnormalities in the context of excess adipose tissue mass, especially visceral adiposity, contributes to the

development of chronic diseases, including type 2 diabetes, cardiovascular disease and certain types of cancer¹⁰⁰. Although premenopausal women are less prone to metabolic-related diseases than men¹⁰⁰, this protection is lost during menopause and is associated with a rapid increase in central adiposity¹⁰⁰, with findings from SWAN showing that the mean rate of increase in fat mass nearly doubles during the decade before FMP¹⁵. Although oestradiol levels are quite variable in women across the life course, expression of adipose *ESR1* is heritable (TwinsUK; narrow-sense heritability estimates $h^2 = 0.29$) and negatively associated with adiposity⁴². Of note, a strong negative relationship between *Esr1/ESR1* and adiposity is similar between females and males from mice to humans^{42,43,101}. *ESR1*, similar to genes associated with mitochondrial function, is reduced in adipose tissue from obese women even before menopause⁴⁴. *ESR1* expression tracks with mitochondrial function in both white and brown adipose^{92,102,103}, as mitochondria-related transcriptional signatures are differentially expressed in adipocytes of healthy monozygotic twins discordant for obesity⁹². Notably, *ESR1* is normalized to lean control values in adipose tissue within 18–24 months after gastric bypass surgery⁴⁴. Studies in mice with selective deletion of ER α from adipocytes demonstrate a causal relationship between oestrogen action in regulating adiposity and glucose homeostasis at baseline and during thermal challenge in the context of biological sex and age^{42,53,104,105}.

Innate immune cells

Over the past decade it has become well accepted that the innate immune system exerts important regulatory control over adiposity and metabolic health. Considering that innate immune cells are resident within, as well as recruited to metabolic tissues from the bone marrow and thymus, these cells must clearly adopt a variety of phenotypes to serve the diverse metabolic demands of these complex organ systems. Innate immune function declines with ageing but heightened basal immune cell inflammation and circulating cytokine concentrations are noted, and these are associated with an increase in metabolic disease risk, especially in menopausal women¹⁰⁶. Rodents harbouring a homozygous *Esr1* null mutation display heightened tissue inflammation, insulin resistance, marked obesity and increased atherosclerotic susceptibility⁵¹. Modulation of inflammatory signalling in macrophages and neutrophils by oestradiol is in large part shown to be ER α -dependent^{51,55,107,108}. ER α -selective deletion from macrophages produces glucose intolerance, insulin resistance, obesity and increased atherosclerotic lesion area in female mice⁵⁵. These myeloid driven phenotypes seem consequent to ER α -controlled regulation of mitochondrial metabolism, reverse cholesterol transport, iron homeostasis, inflammation and wound-healing mechanisms⁵⁵.

Oestradiol action, menopausal hormone treatment and metabolic-related disease

The field has convincingly shown that impairment of oestradiol production and hormone action underpins obesity, insulin resistance and metabolic-related disease in both sexes of humans and rodents. Moreover, a strong impact of *ESR1* on cholesterol and lipid-lowering drug efficacy are noted, as for example, simvastatin was more effective at increasing high-density lipoprotein and reducing total cholesterol in people harbouring *rs2234693* and *rs3798577* *ESR1* variants. These data underscore potential mechanisms contributing to variation in metabolic traits across a female population, as well as sex-biased variability in clinical responsiveness to specific therapeutic interventions aimed at combating metabolic dysfunction. Of note, for a host of drug classes, concern regarding effectiveness, as well as incidence of adverse outcomes in women, is mounting^{109–111}. Clinical studies, including findings from the Women's Health Initiative (WHI), show that menopausal hormone treatment diminishes new-onset diabetes and reduces metabolic dysfunction^{112,113}. An age stratified analysis (46–50 and 55–60 years) revealed significant protective effects of menopausal hormone

treatment at ages closer to FMP; thus, the timing of E2 treatment for maximal therapeutic benefit must be examined¹¹⁴. Considering that there is no other life phase with a comparative magnitude increase of metabolic disease risk, physicians are challenged to address metabolic dysfunction during the menopausal transition.

Future directions and concluding remarks

Although oestradiol and ERs were discovered early in defining the nuclear receptor superfamily, we are still limited in our understanding of the mechanisms governing oestradiol action in metabolic cell types. Over the past decade, research has focused on understanding the tissue contributions of *Esr1* and E2 action on whole-animal physiology, as well as the molecular actions of the receptor, including delineation of ER α -driven transcriptional, proteomic and metabolomic signatures that arise under a variety of challenges, for example oestradiol modulation, ageing, caloric restriction, overnutrition and exercise. Moving forward, it will be important to discern the relative control of oestradiol over metabolism by genomic, nongenomic and nonreceptor-mediated action; however, these studies will require innovative scientific tools for improved interrogation. Additionally careful consideration of effective oestradiol and receptor dosing, as well as timing of ligand–receptor manipulation should be employed (for example, phenotypic differences observed between conventional versus conditional KO models with gene manipulation occurring during development and adulthood). Studies to identify signals for cytosolic localization and protein binding partners of ER α , as well as whether ER α interacts with mitochondrial membranes (outer mitochondrial membrane or internal cristae) are sorely needed, especially in light of the recent observation from the Molecular Transducers of Physical Activity consortium that oestrogen action is a top tissue-conserved pathway (six metabolic tissues studied) differentially expressed following exercise intervention¹¹⁵. Considering that physical activity is a proven strategy for combating metabolic dysfunction, understanding the role of oestradiol/ER α in mediating the health benefits of physical activity seems prudent. These studies reinforce the notion that more robust basic science must be conducted to guide the rational design of new therapeutics targeting ERs in the pre/peri- and postmenopausal life phases. Moreover, improved representation of women in all clinical trials is needed so that studies are adequately powered to evaluate sex-specific differences in disease progression and pathobiology, as well as drug efficacy and safety.

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