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Review

Role of estrogen in the regulation of central and peripheral energy homeostasis: from a menopausal perspective

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Jing Zhu, Yier Zhou, Bihui Jin and Jing Shu

***Abstract*:** Estrogen plays a prominent role in regulating and coordinating energy homeostasis throughout the growth, development, reproduction, and aging of women. Estrogen receptors (ERs) are widely expressed in the brain and nearly all tissues of the body. Within the brain, central estrogen *via* ER regulates appetite and energy expenditure and maintains cell glucose metabolism, including glucose transport, aerobic glycolysis, and mitochondrial function. In the whole body, estrogen has shown beneficial effects on weight control, fat distribution, glucose and insulin resistance, and adipokine secretion. As demonstrated by multiple *in vitro* and *in vivo* studies, menopause-related decline of circulating estrogen may induce the disturbance of metabolic signals and a significant decrease in bioenergetics, which could trigger an increased incidence of late-onset Alzheimer's disease, type 2 diabetes mellitus, hypertension, and cardiovascular diseases in postmenopausal women. In this article, we have systematically reviewed the role of estrogen and ERs in body composition and lipid/glucose profile variation occurring with menopause, which may provide a better insight into the efficacy of hormone therapy in maintaining energy metabolic homeostasis and hold a clue for development of novel therapeutic approaches for target tissue diseases.

Keywords: energy homeostasis, estrogen, glucose, lipid, menopause, obesity

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Introduction

Abnormal energy metabolism may lead to a series of physical disorders and predispose postmenopausal women to obesity, type 2 diabetes mellitus, Alzheimer's disease (AD), and cardiovascular disease.[1] The incidence of metabolic diseases shows a gender-specific character, with females being particularly at risk of age-correlated metabolic pathology.[2,3] Premenopausal women exhibit a healthier metabolic pattern compared to age-matched men. However, in the postmenopausal state, with the absence of estrogen, women experience general variations in glucose and lipid profiles, as well as the redistribution of body fat, triggering a significant increase in metabolic-related diseases and all-cause mortality.[4] These findings verify that estrogen is a fundamental regulator in maintaining female energy homeostasis.

Estrogens, as a category of steroid hormones, include estradiol (E2), estriol (E3), and estrone (E1). In humans, estradiol is the primary circulating estrogen hormone that mediates signals through the intracellular nucleus, plasma, and membrane-associated estrogen receptors (ERs).[5] Estrogen is among the most essential hormones in women and gets involved in the initiation, development, and maintenance of reproductive and physiological functions across the body tissues.[6] With the improved life expectancy and the high prevalence of postmenopausal metabolic dysfunction, the beneficial effect of estrogen (mainly referred to estradiol) on central and peripheral energy balance has gained extensive attention. In this study, we review how estrogen contributes to bioenergetic systems in the brain and whole body through ERs signaling in women. Besides, the choice of a particular

Correspondence to:
Jing Shu
Reproductive Medicine Center, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang 310006, China
shujing@hmc.edu.cn

Jing Zhu
Yier Zhou
Bihui Jin
Center for Reproductive Medicine, Department of Reproductive Endocrinology, Zhejiang Provincial People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China

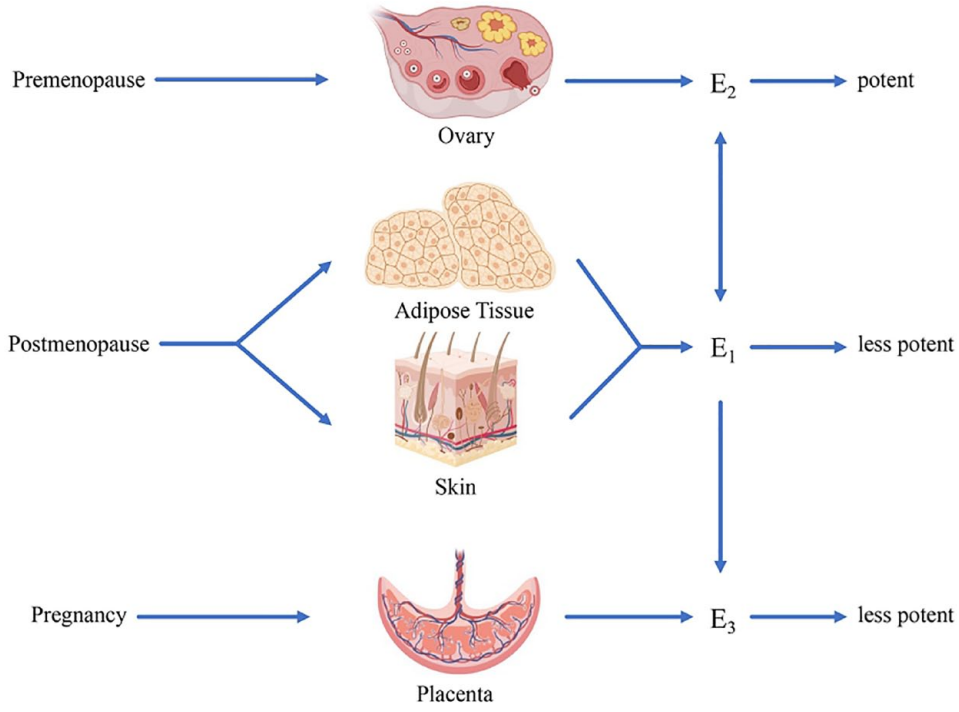

Figure 1. Schematic representation of biosynthesis of estradiol (E2), estriol (E3), and estrone (E1). E2, with the highest affinity to ERs, is primarily secreted by ovarian granulosa cells in premenopausal women. E1 and E3 are the metabolites of E2, both of which are much less potent than E2. Besides, E1 is the main estrogen after menopause synthesized in peripheral adipose and skin tissue, while E3 is mainly produced by the placenta in pregnant women.

regimen, dosage, and timing of estrogen therapy have been discussed, with a special emphasis on its regulation of metabolism and clinical implications.

Estrogen and ERs

Estrogens refer to C_{18} steroids that are derived from cholesterol, catalyzed by the enzyme aromatase, and converted from the C19 precursor, androgen. The aromatase is detected in various human tissues, such as ovarian granulosa cells, adipose and skin fibroblasts, placental syncytiotrophoblast, brain, and bone.[7] With the highest affinity to ERs, E2 is primarily secreted by ovarian granulosa cells in premenopausal women. E1 and E3 are the metabolites of E2, both of which are much less potent than E2.[8] E1, as the main estrogen after menopause, is synthesized in peripheral adipose and skin tissue with precursor androstenedione produced by the adrenal cortex. E3 is mainly produced by the placenta in pregnant women (Figure 1). Orally ingested exogenous estrogen first passes from the intestine to the liver and is rapidly metabolized into less potent E1 before reaching the specific tissue.[9] The first pass decreases the estrogen level in circulation and affects other liver metabolic functions (i.e. coagulation and lipid metabolism).[10] Later, metabolized estrogen in the gut is reabsorbed into circulation through enterohepatic circulation with the help of enteral bacterial flora. Coadministration with drugs that disrupt the gut microbiota, such as antibiotics, may inhibit the effectiveness of estrogen replacement therapy.[11,12] Therefore, it is essential to individually design the route of administration of estrogen replacement therapy and evaluate specific combined medication to avoid drug–drug interaction.

Estrogen signaling is mediated by ERs, which belong to the superfamily of nuclear receptors and act as ligand-activated transcription factors (TFs).[13] ERs have two subtypes: ERα and ERβ. The human ERα is located on chromosome 6 and composed of 595 amino acids, whereas ERβ is located on chromosome 14 with 530 amino acids. Both of them share similar structural and functional features, with six distinct domains.

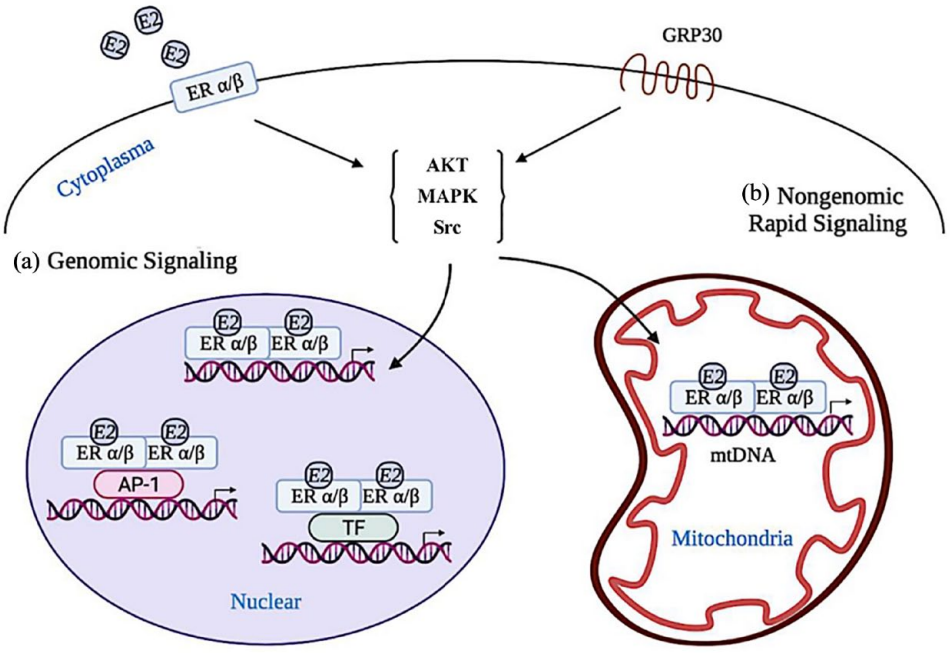

Figure 2. Overview of intracellular 17β-estradiol (E2) signaling. E2 signaling is mediated by ERs, which include two typical isoforms, ERα and ERβ. (a) Genomic signaling involves two different models occurring within hours. E2-activated dimerized ERs directly bind to nuclear ERE on the promotor of target protein regulating transcriptional responses, or modulating specific transcription factors or activator protein 1 indirectly regulating transcriptional responses. (b) Nongenomic ERs rapid signaling occurs within minutes or seconds across the plasma membrane. Member-embedded ERs or G protein-coupled ER (GPR30) are initiated by E2 and subsequently activate multiple signaling pathways, such as Src, MAPK, and AKT signaling cascades, to induce downstream ion fluxes and protein kinases activation. Mitochondria is also the target organelle of E2, where both ERα and ERβ are localized for maintaining cellular bioenergetics. Mitochondrial DNA contains ERE-like sequences, which is activated by E2-ER to regulate mitochondrial function.
ER, estrogen receptor; ERE, estrogen response element.

There are two highly conserved regions, in which one is the DNA-binding domain (region C) with 97% amino acid homology between the ERs, and the other is the ligand-binding domain (region E with 56% identity) harboring a hormone-binding site with a dimerization interface and ligand-dependent transactivation function (AF-2).[14] The distribution of ERs is tissue biased and cell specific. Although both ERs are widely expressed in the brain and nearly all tissues of the body, ERα is predominate in the uterus, hypothalamus/pituitary gland, breast, liver, skeletal muscle, bone, and adipose tissue (AT) where ERβ plays a subordinate role, whereas ERβ is considered to be critical in ovary, gastrointestinal, cardiovascular and central nervous systems (CNSs), etc.[15] Even in a single tissue (e.g. in the ovary), ERα is predominant in theca cells and ERβ is found in granulosa cells.[16] Thus, the differential expression of the ERs is also the foundation for exploring selective estrogen receptor modulators (SERMs), which bind to a certain subtype of ERs to induce either agonist or antagonist effects.[17] Monomeric ER is activated by E2 to form homo- or heterodimer regulating followed transcription. In heterodimer, ERα is reported as the dominant partner.[18]

Estrogens are lipid-soluble and easily diffuse through the cell and nuclear membrane, attaching to dimerized ERs at the nuclear, mitochondria, and the peri-membrane (Figure 2).[19] ER-mediated nuclear signaling, as the classic cellular response to E2, includes two different models occurring within hours. Estrogen response element (ERE)-dependent signaling pathway is that E2-activated dimerized ERs directly bind to ERE on the promotor of target protein regulating transcriptional responses. The other ERE-independent signaling pathway is that E2-activated ERs modulate specific TFs (such as Fos/Jun) or activator protein 1 (AP-1) and bind to the TF/AP-1 response element of the target protein indirectly regulating

transcriptional responses.[20] In comparison to ERα, ERβ has a lower affinity to ERE.[21] Except for the above genomic signaling, extranuclear events are mediated by nongenomic ERs rapid signaling that occurs within minutes or seconds across the plasma membrane. With the exposure of E2, member-embedded ERs or G protein-coupled ER (also called GPR30) are initiated and subsequently activate multiple signaling pathways, such as Src/ phosphatidylinositol-3-kinase (PI3K), Ras/Raf/MEKK/ extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK)/ERK, PI3K/protein kinase B (AKT), cAMP/ Protein kinase A (PKA), and JNK signaling cascades, to induce downstream ion fluxes and proteins kinases activation.[22–24] Here, whether GPR 30 is a kind of member ER or a kind of G protein coupled with the original ER remains controversial.[25,26] In recent years, other types of membrane estrogen receptors (mERs) have been reported. ER-X is reported as a new plasma membrane-associated estrogen-binding protein that participates in estrogen-activated MAPK cascades to alleviate brain injury.[27] Gαq-coupled mER (Gαq-mER) activated by E2 or selectively targeted by STX, a diphenylacrylamide compound that does not bind to either ERα or ERβ, modulates the gamma-aminobutyric acid type B signaling and induces both opposite effects on hypothalamic orexigenic and anorexigenic neurons.[28,29] Recent evidence shows that mitochondria are also the target organelles of E2 where both ERα and ERβ are localized for maintaining cellular bioenergetics.[19] Meanwhile, mitochondria DNA (mtDNA) contains ERE-like sequences, indicating the regulation of E2 on mtDNA transcription *via* ERs signaling. Despite a large number of studies, the molecular mechanism of E2 signaling and the role of ERα or ERβ in regulating cellular events of phosphorylation, acetylation, glycosylation, and ubiquitination is still a developing area of investigation.

Estrogen and central energy homeostasis

Many different cell types in the human brain, including astrocytes and neurons, may express aromatase.[30] Thus, E2, as an important modulator of central bioenergetics, may exert its effect by crossing the blood–brain barrier (BBB) into the brain from the peripheral circulation, or being made from cholesterol within the brain.[31] ERα and ERβ, which serve different roles in the brain, are widely expressed in the hypothalamus, hippocampus, neocortex, preoptic area, septum, amygdala, and the periaquaductal central gray.[32] The central bioenergetics system is modulated by E2 signaling mainly *via* (1) regulating glucose metabolism (the predominant preference in the brain) and providing adenosine triphosphate (ATP) and precursors for sustaining physiological brain function and (2) controlling the energy balance between energy expenditure and energy intake.[33]

Estrogen regulation of central glucose metabolism

As revealed by recent clinical studies, heightened estrogen levels are correlated with increased cerebral glucose utilization, thereby affecting cognitive and behavioral functions.[34–37] Estrogen induces a series of nongenomic signaling pathways including MAPK, PI3K/AKT, c-Fos, Protein kinase C (PKC), and Ca2+ influx in the brain to sustain mitochondria function and regulate the glucose transports (GLUTs) into the cell, aerobic glycolysis (glycolysis coupled to the citric acid cycle) derived oxidative phosphorylation and ATP generation.[24,38,39]

Glucose enters into the brain from the blood by utilizing its concentration gradient, which propels glucose-facilitated transport across the plasma membrane *via* GLUTs. GLUTs consist of three subfamilies with a total of 13 family members (GLUT1-12 and *H*+/myo-inositol transporter), among which GLUT1 and GLUT3 are found most popular in the brain, while other isoforms, such as GLUTs 4, 6, 8 have also been detected in brain with minor expression.[40] Neuronal energy deficit brought on by GLUTs may play an important role in AD development.[41] Meanwhile, scientific evidence from animal studies suggests a potential protective mechanism of estrogen associated with GLUTs. Ovariectomy (OVX) may directly decrease the GLUT1 and GLUT3 expression in the rat's brain and cause impaired insulin sensitivity and oxidative stress.[42,43] *In vivo* treatment with E2 demonstrates a notable augmentation in the uptake of 2-deoxy-[14C]glucose into the BBB endothelial cells of ovariectomized female rates, implying that the observed effect of E2 is attributable to its regulatory influence on GLUT-1 mRNA and protein expression.[44] Given that GLUT is insulin sensitive, so the neuroprotective estrogen upregulates insulin growth factor-1 (IGF-1) signaling *via* the synergistic effect of ERs and IGF-1 receptor, activates MARK and

PI3K cascades, and increases the GLUT3,4 expression in cerebral cortical neurons of ovariectomized rhesus monkeys.[45]

It has been reported in wild-type mice with an age-dependent decline of aerobic glycolysis enzymes and a concomitant decrease in lactate. Lactate is the metabolite of aerobic glycolysis and the substrate fuel for aerobic respiration that is associated with memory consolidation in the frontal cortex.[46] E2 promotes neuronal aerobic glycolysis by activating hexokinase (HK), phosphofructokinase, and pyruvate kinase within 4 h in rat brains.[47] While HK is considered to bind to voltage-dependent anion channel directly coupling intramitochondrial ATP synthesis, E2 has been announced to activate Akt, increase HK activity and herein, and trigger enhanced glucose metabolism *in vitro* study.[2,48,49] As shown by additional evidence, E2 enhances glycolytic activity by increasing aconitase, decreasing malate dehydrogenase, and increasing glutamate dehydrogenase and glutamate oxaloacetate transaminase-2 in ovariectomized female rat.[50]

Furthermore, the E2 signal has been identified as one of the major signals that converge upon mitochondria to exert its neuroprotective effect. Mitochondria malfunction may cause many neurocognitive and neurodegenerative disorders, such as AD, depression, and anxiety, which show a sex-specific prevalence.[51–54] Proteomic analysis of brain mitochondria of female rats indicates that E2 regulates the expression of pyruvate dehydrogenase (PDH), a pivotal enzyme that transforms the pyruvate to acetyl CoA, provides substrate in the citric acid cycle, concomitantly increases oxidative phosphorylation and ATP synthase, and decreases β-oxidation.[50] According to another *in vivo* data, E2- and progesterone-treated rats brain mitochondria display enhanced respiratory function coupled with increased expression of the electron transport chain complex IV (cytochrome C oxidase).[55] Notably, the research by Irwin *et al.*[56] demonstrates that medroxyprogesterone acetate (MPA) inhibits the upregulation of brain mitochondrial activity by E2 and induces a decrease in the mitochondrial expression of PDH, cytochrome oxidase, ATP synthase, manganese-superoxide dismutase, and peroxiredoxin V in ovariectomized female rats, suggesting that different hormone regimens may exert opposing effects on mitochondria function.[56] Moreover, animal data show that E2 has a protective effect on the mitochondria against the accumulation of amyloid beta and hyperphosphorylation of tau, which is involved in increased mitochondrial calcium uptake and decreased ATP production.[57] Excessive intracellular calcium rise of hippocampal neurons in rat fetuses may promote glutamate excitotoxicity, which is attenuated by E2 treatment *via* improvement of the mitochondrial sequestration of cytosolic Ca (2+) coupled with an increased expression of anti-apoptotic protein Bcl-2 to sustain the Ca(2+) load tolerance.[58]

Both ERα and ERβ were examined with SERMs in animal experiments, each of which displayed an independent capability in upregulating the mitochondria proteins. Targeting ERβ exhibits greater efficacy in mitochondrial respiration.[59,60] Recent studies have also highlighted the role of ERβ in triggering more sensitive mitochondrial calcium permeability in females than in males.[61]

Due to the pivotal function of mitochondria in central bioenergetics, many studies have been conducted to develop pharmaceuticals targeting the complex mechanism of mitochondria.[62] Currently, the treatment of neurodegenerative disorders by mitochondrial transplantation is also a hot topic.[63] However, it is noteworthy that many discoveries are based on animal research, raising questions about whether they can actually be applied to humans.

Estrogen regulation of central appetite and energy expenditure

Energy homeostasis, a delicate balance between energy expenditure and energy intake, is regulated by two coordinated networks, namely homeostatic and hedonic neural circuits.[64] Homeostatic regulation of energy balance is mainly reliant on hypothalamic and brainstem-associated neuronal populations, including those in the arcuate nucleus (ARC), lateral hypothalamus (LH), ventromedial nucleus (VMN), dorsomedial nucleus, and paraventricular nucleus, which are modulated by E2 signaling, activate ER, and Gαq-mER to trigger later signaling cascades involving PI3K, PKC, PKA, and neuronal nitric oxide synthase, deliver orexigenic or anorexigenic signals to stimulate, or suppress the energy intake and the energy expenditure[65] (Figure 3). ERα is dominant in hypothalamic metabolic regulation.[66] The ERα mutant mice that only signal *via* nonclassical pathways are shown to be sufficient for restoring

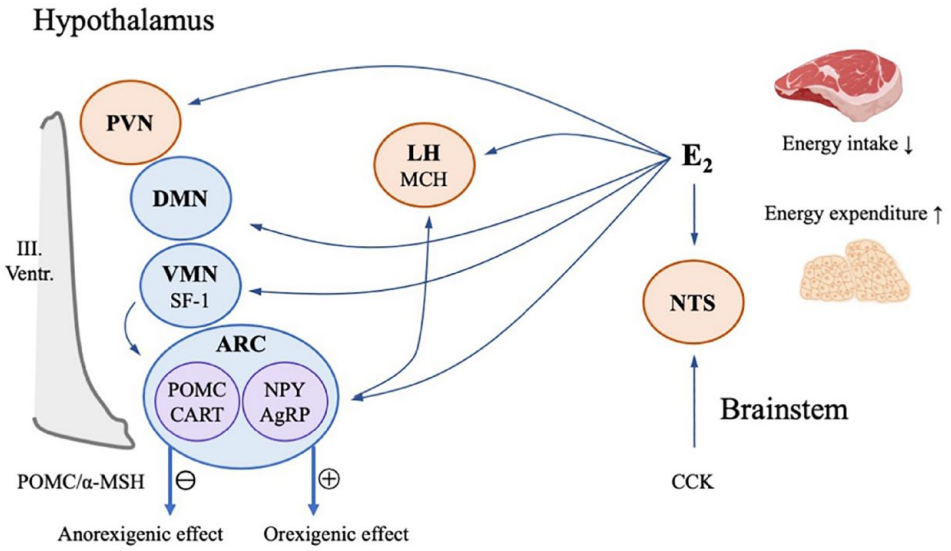

Figure 3. Model of 17β-estradiol (E2)'s homeostatic regulation of energy balance in the brain. Brain regulation of energy homeostasis is mainly reliant on hypothalamic and brainstem-associated neuronal populations, including those in the arcuate nucleus (ARC), lateral hypothalamus (LH), ventromedial nucleus (VMN), dorsomedial nucleus, and the paraventricular nucleus, which are modulated by E2 signaling, and deliver orexigenic or anorexigenic signals to stimulate or suppress the energy intake and the energy expenditure. Proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript neurons and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons in ARC may regulate the body energy status through POMC/α-melanocortin stimulating hormone signaling. POMC neurons are impinged by steroidogenic factor-1 neurons in the VMN, while NPY/AgRP neurons project to melanin-concentrating hormone neurons in LH. Nucleus tractus solitarius in the brainstem, which receives abdominal vagal afferent projections activated by the peptide cholecystokinin, may modulate the feeding inhibition effect *via* E2 signaling.

metabolic deficit to normal or near-normal values, indicating that the membrane-based signaling pathway also plays a pivotal role in maintaining energy homeostasis.[28,67]

Evidence shows a gender difference in food cravings, binge eating disorders, and obesity.[68] Women are 3% more likely to be overweight than men. In addition, female food consumption fluctuates across the menstrual cycle, as observed by preclinical and clinical studies. Women in the luteal phase present an increased food craving and eating behavior with a lower E2 level compared with the follicular phase.[69] As suggested by animal experiments, E2 might attenuate the cannabinoid-induced hypothermia, hyperphagia, and the decrease in glutamatergic neurotransmission at proopiomelanocortin (POMC) neurons in the ARC of ovariectomized female guinea pigs.[70] POMC neurons, impinged by steroidogenic factor-1 neurons in the VMN, are critical anorexigenic synapses. From the data on mice and rats, it could be observed that the activated POMC neurons release satiety mediator α-melanocortin stimulating hormone signaling (α-MSH), β-endorphin, as well as co-express cocaine- and amphetamine-regulated transcript, which are involved in the glucose metabolism.[71,72] Conversely, together with agouti-related peptide (AgRP) co-expressing neurons in ARC, neuropeptide Y (NPY) promotes the central orexigenic or appetite-stimulating effect, ultimately inducing feeding and reducing energy expenditure through the inhibition of POMC/α-MSH signaling.[73] As elucidated by studies, NPY neurons can be modulated by E2. For example, increased NPY expression induced by OVX can be reversed by E2 administration in rats.[74] Due to its location, the ARC is in direct contact with circulating hormones, sustaining energy homeostasis through the communication of the energy status between the body and brain.[65]

In addition to ARC neurons, other hypothalamic neurons also participate in E2's regulation of homeostatic energy balance. Melanin-concentrating hormone (MCH) neurons are located in the LH area, receive inputs from NPY/AgRP neurons in ARC, and synergistically induce

the orexigenic effect. MCH is upregulated when E2 is low.[75] As claimed by Musatov *et al.*,[76] site-specific silencing of ERα in the ventromedial hypothalamus (VMH) decreases the E2-induced energy expenditure and leads to weight gain and visceral fat accumulation in female mice and rats.[76] Another animal study indicates that the feeding inhibition effect may also be mediated by ERα signaling in nucleus tractus solitarius, an area of the brain that receives abdominal vagal afferent projections, which may be activated by the peptide cholecystokinin, released by duodenal I cells.[77]

Alongside the homeostatic neural circuits, energy homeostasis is also modulated by hedonic feeding behavior, namely reward-based food intake. Multiple evidence suggest that reward and drug addiction converge upon a common pathway to mediate motivated behavior within the limbic system.[78,79] The hedonic regulation of feeding is reliant on the mesolimbic dopamine (A_{10}) neurons that emanate from the ventral tegmental area (VTA) and project onto other regions, including the nucleus accumbens, prefrontal cortex, hippocampus, and amygdala. ERs are expressed in VTA. Activation of ERα enhances the ethanol-induced VTA sensitivity and causes binge-like alcohol drinking by female mice, not males.[80] Women present more rapid drug addiction and greater withdrawal response, due to increased dopamine release by E2 stimulation in the dorsolateral striatum, but not in nucleus accumbens.[81] Interestingly, intra-VTA microinjection of E2 conversely shows a significant decrease in food-motivated behavior of female rats.[82] Therefore, these variable results between the drug *versus* food rewards in women, as well as the sex differences in motivated behavior, promote us to further explore the role of estrogen in regulating hedonic feeding behavior.

Estrogen and peripheral energy homeostasis

In addition to the brain, estrogen is closely related to energy homeostasis in the whole body. During the reproductive age, the average level of circulating E2 is 100–250 pg/mg. However, along with the cessation of oocyte production, the E2 level declines up to 10 pg/ml.[83] Clinically, menopause is diagnosed with 12 months of amenorrhea following the final menstrual period. Epidemiological studies spanning 35 countries reported that the overall average age of menopause for women with natural menopause is 48.8 years, with regional differences.[84] The change in E2 with the menopausal transition may be related to a series of dysregulation of peripheral lipid and glucose metabolism, which affects the body weight, body fat redistribution, fatty acid metabolism, various lipid profiles, and adipokines circulating in serum, and leads to an increase in the development of type 2 diabetes mellitus, hypertension, and cardiovascular diseases in postmenopausal women.[85]

Estrogen, obesity, and adiposity

Obesity, defined as the body mass index (BMI, weight in kg/height in m^2) $\geqslant$30, resulted from an imbalance between energy expenditure and energy intake. It was reported that women are twice as likely to suffer from obesity than men worldwide.[86] Earlier, it is commonly believed that weight gain in postmenopausal women is attributed to estrogen deficiency.[87] However, according to the *2016 Guideline of the International Menopause Society*, multiple studies have obtained consistent results that the weight gain seen in midlife women is attributed to aging and environmental factors, such as inactivity, urbanization, higher parity, etc., not menopause.[88] Instead, the alternation of the E2 milieu at menopause is mainly associated with a significant increase in total fat mass and abdominal obesity, especially visceral adipose deposition.[89,90] Abdominal obesity, defined as a raised waist circumference, is confirmed to be associated with higher cardiovascular mortality compared with high BMI-defined obesity.[4,91,92]

The distribution of regional AT is different between women *versus* men. The sexual dimorphism in total fat distribution is attributed to sex-linked genes.[93] Premenopausal women hold a relatively healthier glutei-femoral pattern of fat accumulation than age-matched men. After menopause, women experience a significant increase in total fat mass and redistribution of AT, resulting in a high risk of abdominal obesity. Although the underlying process is not yet fully understood, some studies have suggested that postmenopausal visceral and non-subcutaneous AT fat deposition is caused by tissue-specific control of estrogen through ERs signaling.[94,95] Another study proposed that E2 exerts a lipolysis effect by upregulating α2A-adrenergic receptors in human subcutaneous AT, rather than visceral AT.[96]

Both ER isoforms are present in human AT, but their distribution is not equal, with a large predominance of ERα expression. For instance, it was reported from a study of overweight-to-obese premenopausal women that ERα is dominant in abdominal subcutaneous AT, whereas ERβ is dominant in gluteal fat.[97] As suggested by animal research, the age-associated E2 deficiency alters the ERα/β ratio to greater ERβ in visceral AT of rats and causes increased adiposity.[98] Apart from that, the expression of ERα is identical between sexes, whereas ERβ level is higher in women than in men. In an *In vitro* study, E2 upregulates both ERα and ERβ expression in female subcutaneous adipocytes, but only ERα expression in both subcutaneous and visceral adipocytes in men.[99] In addition, ERα but not ERβ-deficient male mice develop obesity after sexual maturation.[100] This sex dimorphism in the distribution of ERs may explain the android and gynoid body shape between men and women. ERs mediate crucial estrogen signaling pathways in both women and men. Notably, the distinct estrogen levels, tissue-specific distributions of ERs, and intricate interactions with other hormones, such as testosterone, bestow distinct physiological and developmental effects in each sex.[101,102]

It was previously believed that ERα and ERβ perform opposing roles in the metabolism of glucose and lipids.[103] As demonstrated by Davis *et al.*,[104] selective ERα silence in AT of adult mice increases adiposity and inflammation. Another piece of evidence indicates that ERα signaling has a protective effect on white AT of both sexes, and ERα-knockout (αERKO) mice show enhanced fat accumulation, namely adipocyte hypertrophy and hyperplasia.[105] The observations discussed above lead to certain speculation that with the absence of ERα, this unhealthy adipose phenotype may be regulated through ERβ signaling.[2] With a deepened understanding of ERβ, positive results have been reached in some investigations that specifically address the topic.[106] The activation of ERβ may lead to an anti-obesity development with increased mitochondrial function and energy expenditure in brown AT of mice, as mentioned by Ponnusamy *et al.*[107] According to the research of Yepuru *et al.*,[108] ER-β-selective ligands reduce the fat mass in an animal model of OVX- and high-fat diet-induced obesity.[108] The conclusion of these studies supports that both ERα and ERβ participate in the anti-lipogenic action of estrogens and may have overlapping yet unique roles.[109,110] To limit lipogenesis, E2 may also modulate the synthesis of adipose depot Lipoprotein lipase.[111] Moreover, vascular endothelial growth factors and peroxisome proliferator-activated receptor gamma (PPARγ) are involved in the regulation of E2 signaling in lipid deposition.[111,112]

Estrogen regulation of glucose profile

Insulin plays a pivotal role in maintaining central and peripheral glucose metabolism in women. The EPIC-InterAct study concluded that menopause occurring before 40 is associated with a higher risk of type 2 diabetes than that after the age of 50.[113] E2 mediates a protective effect against diabetes and AD by regulating insulin biosynthesis and release, insulin sensitivity, and pancreatic β-cell preservation.

In pancreatic islets, it was reported that postmenopausal women have a relatively lower insulin secretion, insulin elimination, and plasma C-peptide response compared with premenopausal women, whereas there is no significant variation in fast plasma glucose and insulin concentration between them.[114] Exposure to physiological level E2 may increase the β-cell insulin release, insulin content, and gene expression without the changes of pancreatic β-cell mass, according to the mice experiment by Alonso-Magdalena *et al.*[115] Consistent with these findings, in rodent models, E2 treatment also attenuates the type I and II diabetes-induced oxidative stress, lipotoxicity, and amyloid polypeptide toxicity in pancreatic β-cell.[20] The pancreatic β-cells of both humans and rodents express ERα, ERβ, and GPER. The protective effect of E2 on pancreatic islets is sustained mainly through a rapid extranuclear pathway involving Src, ERK, and NeuroD1.[20,116,117]

Insulin resistance is a status in which pancreatic islets pathologically hyper-secrete insulin to induce glucose uptake, and it is primarily associated with abdominal obesity. Therefore, E2-replete women with regular menstruation present higher insulin sensitivity normalized to lean mass than the age-matched men.[109,118] The study by Kim *et al.*[119] also suggested that insulin resistance varies depending on the menopause status. E2 improves insulin resistance, resulting in decreased glucose uptake in insulin sensitivity organs, especially AT and skeletal muscle.[120] Skeletal muscle is known as the primary tissue

responsible for oxidative metabolism and glucose disposal. Saengsirisuwan *et al.*[121] reported that OVX mice have lower insulin-activated GLUT in skeletal muscle and exhibit features of insulin resistance syndrome. According to a later study by Ribas *et al.*,[122] muscle-specific αERKO mice are associated with impaired glucose homeostasis and increased adiposity with dysfunctional mitochondria in muscles. Both ERs are expressed in skeletal muscle, with ERβ predominating in mice.[123] ERα and ERβ exert varying effects on GLUT4 expression. Barros *et al.*[124] reported that ERβ has a suppressed role in GLUT4 expression in muscles, which could contribute to insulin resistance in male mice. Gorres *et al.* stated that ERα agonist PPT enhances the GLUT four expression, insulin action, and glucose uptake in skeletal muscles of OVX mice.[125] Hence, compared with ERβ, the positive role of ERα in glucose metabolism in skeletal muscle is relatively clear. In addition, another essential strategy to treat insulin resistance is to eliminate the excess free fatty acids (FFA) in the liver that are released from the abdominal visceral fat depot. αERKO mice show significant hepatic insulin resistance with upregulating in hepatic lipid biosynthesis and downregulating lipid transport.[126] Consistent with this observation, E2 treatment of the high-fat diet mice has decreased body weight, improved glucose tolerance and insulin sensitivity closely correlated to suppressed lipogenic genes in white AT and liver, and decreased hepatic expression of glucose-6-phosphatase.[127] The animal experiment by Gao *et al.*[128] indicated that E2 administration improves glucose tolerance and insulin sensitivity to glucose in ob/ob mice through activating hepatic ERα/Stat3 signaling.[128] Therefore, it is speculated that E2 deficit influences glucose homeostasis in the whole body, especially AT, skeletal muscle, and liver accompanied by impaired glucose utilization and ectopic lipid accumulation.

Notably, several *in vitro* and *in vivo* studies have emphasized that E2 needs to stay within a certain physiological concentration to maintain insulin sensitivity, otherwise, excessive E2 level may conversely reduce GLUT4 expression in muscle and overproduce insulin signaling, which subsequently provokes insulin resistance in the muscle and liver, as well as β-cell exhaustion.[129,130] Postmenopausal high endogenous E2 level is associated with insulin resistance, glucose tolerance, and development of type 2 diabetes.[131–134] Interestingly, hormone therapies on postmenopausal women or surgically ovariectomy primates show different consequences: conjugated equine estrogens (CEE) alone have a beneficial effect on adipocyte size with no other adverse effects, whereas additional adding dose-dependent MPA may harm insulin resistance.[135–137] Therefore, the question of whether there is a maximum concentration at which estrogen may exert a positive effect is still open. The underlying mechanism of E2 in regulating glucose homeostasis is not fully understood, particularly given the disparate research samples, multiple types and routes of hormone therapy, and various testing standards for insulin resistance.

Estrogen regulation of lipid profile

Another noticeable adverse change arising with menopause is the dysregulation of lipid metabolism in the liver and plasma lipid profile, which accelerates the process of fatty liver and atherosclerotic plaque formation with an increased risk of later cardiovascular diseases.

The Study of Women's Health Across the Nation (SWAN), which recruited 3302 women aged from 42 to 52 in 1996 with 17 visits through 2017, reported a sharp increase in apolipoprotein B, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TGs), lipoprotein(a) in late peri- and early postmenopausal stage, as well as high-density lipoprotein cholesterol (HDL-C). Subsequently, serum HDL-C levels gradually flatten till late post-menopause.[138,139] Consistent with the SWAN study, elevated LDL-C, TGs, and TC levels were well recognized to be associated with menopause status in many other studies.[140,141] However, the conclusions about changes in HDL-C during menopause are inconsistent, with some studies that report HDL-C to be maintained or slightly decreased.[138,142,143] As argued by Anagnostis *et al.*,[144] postmenopausal women have a more atherogenic lipid profile with lower HDL-C subfractions 2 compared with premenopausal women. According to Zago *et al.*,[143] increased oxidized HDL in postmenopausal women leads to an impaired protective effect against LDL oxidation, which is independent of HDL-C plasma levels. Hence, measured serum HDL-C level may not fully reflect other metrics of HDL related to menopause alterations.[145]

The circulating lipid profile is usually not directly absorbed from the gut but released into the blood after being processed by various tissues, especially the liver. The liver is the most important organ where TG, TC, and fatty acids are regulated to meet the physiological needs of the whole body. During the menopausal transition, increased FFA releases from AT, then transports to the liver to accelerate the synthesis of TGs rich very-low-density lipoprotein (VLDL) particles and subsequently, leads to enhanced export of VLDL-TGs in the liver, as well as the VLDL-TGs clearance rate.[146,147] More than 1000 human liver genes have a sex-biased expression, especially the genes related to lipid metabolism and cardiovascular diseases, indicating that the liver is the primary target organ of E2.[148,149] Meanwhile, ERs coupling lipid metabolism in the liver was reported to associate with the reproductive cycle in a mouse model.[150] As mentioned by several studies, oral administration of micronized estradiol increases VLDL production, whereas transdermal E2 has no influence on VLDL production, suggesting that hepatic processing is the primary cause of VLDL-TGs elevation due to estrogen action.[147] Both genomic and nongenomic signaling get involved in the E2's regulation of the liver. Chen *et al.*[151] claimed that the knockdown of estrogen-related receptor γ in mice reduces the hepatic VLDL-TGs secretion and leads to lipid accumulation in the liver with non-alcoholic fatty liver disease, which is mediated *via* phospholipase A2G12B. E2 treatment with hepatic knockout ERα plus OVX mice has no protective effect against insulin sensitivity, lipogenesis, and liver TGs export. However, the mice do not develop adiposity, which may be reliant on the maintenance of E2 signaling in the CNS and other tissues.[152]

E2 is also supposed to have a protective effect against fatty plaque formation by regulating cholesterol biosynthesis, uptake and reverse cholesterol transport (RCT) from peripheral tissues back and excreted by bile. The RCT is performed by HDL, which inhibits the accumulation of LDL-C. As suggested by Pedram *et al.*,[153] E2 agonist PPT activates the membrane ERα signaling to induce adenosine monophosphate-activated protein kinase to phosphorylate sterol regulatory element-binding factor 1, and consequently prevents the cholesterol content synthesis in the mice liver. Furthermore, HDL mediates cholesterol efflux from foam cells. The cholesterol and cholesteryl esters are removed either directly through the hepatic scavenger receptor class B member I or transferred *via* cholesteryl ester transfer protein to LDL particles. Furthermore, free cholesteryl is released and excreted by bile.[154] According to the work by Wang *et al.*,[155] E2 stimulates E2/ERα/SREBP-2 pathway in mice to increase the cholesterol secreted into bile.

Estrogen regulation of adipokine

Leptin

Leptin is a protein hormone produced mainly by white adipocytes. The secretion of leptin is proportional to the adiposity of the body. Crossing the BBB, leptin may regulate the central food intake and energy expenditure with receptors in the hypothalamus and brainstem.[74,156,157] The leprb is the most important leptin receptor mainly located in VMH and ARC, which modulates various aspects of energy homeostasis, such as glucose balance, satiety, and hedonic eating.[158] Both E2 and leptin are critical hormones in maintaining the body's energy homeostasis. However, many studies have different opinions over whether there is a cross-talk in CNS between E2 and leptin. As pointed out by Bennett *et al.*,[159] E2 decreases the expression of leptin receptors in the hypothalamus and the changes in total leptin level in rats are inversely proportional to circulating E2 levels in the estrous cycle. Clegg *et al.*[156] reported that adding E2 directly in the female rats' brain increases intra-third ventricular leptin sensitivity. Springer *et al.* analyzed 20 PubMed/Medline articles about the relationship between hormone therapy, leptin, and adiposity in healthy postmenopausal women. As shown by the results, there is no solid evidence verifying that E2 treatment changes circulating leptin levels or improves leptin action in postmenopausal women.[160] Kim *et al.*[161] also shared a similar result in mice experiment that E2 has a minimal direct effect on leprb in mediobasal hypothalamus. Independent of leprb/STAT3 signaling, E2 may still exert its anorexigenic effects in female mice.[161]

Leptin regulates peripheral metabolic processes of glucose and lipids that are typically relevant to the pancreas, liver, skeletal muscle, ATs, immune cells, and cardiovascular system.[162] It was reported that obese postmenopausal women have worse insulin resistance and elevated leptin level.[163] Based on human data, Norata *et al.*[164] also suggested that the leptin/adiponectin ratio is a stronger predictor of cardiovascular diseases than

single adipokine. The prospective, longitudinal study of Di Carlo *et al.* evaluated 44 healthy postmenopausal women who randomly received either transdermal E2 plus nomegestrol or no treatment. As demonstrated by the results, serum leptin as well as the total and percent fat mass is significantly increased 1 year after the study in untreated women, while transdermal E2 treatment shows no changes in leptin as well as body mass throughout the study.[165] Chu *et al.* compared oral and transdermal E2 treatment of obese postmenopausal women with metabolic syndrome (MBS). The transdermal E2 group shows a similar result as the aforementioned study, whereas the oral E2-treated women have an increased leptin level, resulting in an increased leptin/adiponectin ratio with impaired insulin resistance.[166] This once again indicates that different routes of E2 administration should be selected according to each woman's individual condition of each woman.

Adiponectin

Adiponectin is an insulin-sensitive polypeptide hormone produced mainly by adipocytes.

Similar to leptin, the effect of adiponectin appears to be both centrally and peripherally mediated.[167] Multiple studies demonstrated that adiponectin has an anti-diabetic, anti-atherogenic, anti-inflammatory, and anti-oxidative effect mediated primarily by two receptors, adipoR1 and adipoR2, which activate the downstream signaling, including 5'-adenosine monophosphate (AMP)-activated protein kinase and PPARs.[168–171] The action of adiponectin seems to be bidirectional modulated. Low adiponectin plasma levels are known to increase the risk of MBS, obesity, and cardiovascular diseases throughout the postmenopausal era.[172,173] It was found that increased plasma adiponectin is an independent risk factor for the onset of AD and all-cause dementia in women in a large-scale study conducted in 2012.[174] De Franciscis *et al.*[175] also mentioned that serum adiponectin levels are associated with cognitive decline in postmenopausal women.[175]

Both leptin and adiponectin levels are higher in women than in men.[162,176] According to one study of Africa America women, visceral AT is inversely associated with adiponectin level, but no correlation is shown in men.[177] In an *in vitro* experiment by Foryst-Ludwig *et al.*,[178] it was revealed that ERβ decreases the PPARγ transcription activity, which regulates adiponectin promoter in white AT. Whether the adiponectin level changes during the menopause transition, there is still no consistent conclusion. Some studies reported a negative association of E2 with adiponectin level,[179,180] whereas others showed no significant difference in adiponectin levels between pre- and post-menopause women.[181,182] Unlike leptin, Chalvatzas *et al.*[183] argued that oral estrogen administration does not affect adiponectin levels, whereas Chu *et al.*[166] suggested that adiponectin levels increase when transdermal E2 treatment is conducted on obese postmenopausal women with MBS.

Estrogen, timing, and hormone therapy

Menopause has long been considered a natural aging process in women along with menopausal disorders, such as hot flashes, night sweats, and insomnia, which affect not only the life quality but also long-term health with an improved incidence of obesity, osteoporosis, urogenital tract atrophy, and cardiovascular diseases.[184] From the first use of bovine ovarian for relieving menopausal symptoms to today's standard menopausal hormone therapy (MHT), the concept that women's aging needs medical attention is gradually gaining popularity.[88,185] However, the history of understanding estrogen supplements and MHT is full of twists and turns. The first severe blow in the use of estrogen supplements occurred in the 1970s when it was reported that a sharply increased risk of endometrial cancer was associated with estrogen therapy.[186] Later, this risk was counteracted by extra progestin addition in women with a uterus, which initiated the revival of MHT usage. However, in the 1990s, the famous Women's Health Initiative (WHI) trial enrolled over 16,000 postmenopausal women, used conjugated estrogen plus MPA for women with an intact uterus and reported that MHT worsens the risk of breast cancer, pulmonary embolism, stroke, and coronary heart disease. Throughout the decade from 2000 to 2009, the long-term impact of the WHI caused a continued decline in MHT prescription, and the treatment regimen shifted to favor low-dose oral or vagina preparations.[187] Furthermore, age-stratified analysis of the 13-year follow-up data in the WHI study yielded a more complete evaluation of MHT and proposed the 'timing hypothesis'.[188] Women should initiate the MHT less than 10 years after menopause or within 60 years of age so that the benefits of symptom control and

disease prevention outweigh the risks. Otherwise, MHT may stimulate different biological processes of vascular endothelium, smooth muscle cells, and inflammatory cells on established atherosclerosis inversely, leading to an increased risk of cardiovascular diseases.[189,190]

The concept of the 'timing hypothesis' also exists in E2's protective effect against the development of AD.[191,192] As pointed out by Brinton,[193] MHT should begin early in menopause when neurons are still in a healthy state, otherwise MHT may have no benefits but lead to a detrimental effect on the brain.[193] Henderson and Sherwin[194] suggested that although MHT should not be used to improve cognitive function, a short-term cognitive benefit is observed when initiating MHT at the time of surgical menopause.[194]

As claimed by Li *et al.*,[195] earlier puberty timing status is correlated with obesity. Later menarche was reported with a lower risk of type 2 diabetes and cardiovascular diseases (Zhang *et al.*, 2020; Qiu *et al.*, 2013).[196,197] Another study focused on the timing of pharmacologic sex hormone use during pregnancy. Indeed, oral contraceptive or diethylstilbestrol (DES) use during pregnancy is strongly associated with offspring overweight, especially when the oral contraceptive is used in the first 2 months of pregnancy or DES is used between months 3 and 5.[198] The above studies indicated that earlier elevated endogenous E2 levels or earlier exposure to exogenous estrogen may cause long-term negative effects on the energy metabolism of the body.

In addition to timing, the type, dosage, and route of the MHT regimen are equally important.[199] Godsland reviewed 248 studies about the effect of different MHT formulations on lipid profile and found that in all cases, estrogen alone decreases LDL and TC, and increases HDL-C; oral estrogen increases TG, while transdermal estrogen lowers TG. In addition, adding different types of progestogens may have the opposite effect on the estrogen-induced increase in HDL and TG. Tibolone decreases HDL-C and TG levels.[200] The above beneficial effects on LDL-C, TC, lipoprotein(a), insulin resistance, and harmful effects on TG are attributed to the hepatic first-pass effect.[201] Therefore, different routes of administration may influence hepatic lipid metabolism and energy homeostasis.[10] The ancillary Cognitive and Affective Study of the Kronos Early Estrogen Prevention Study also suggested that oral CEE has a beneficial mood effect, but transdermal CEE does not.[202] Beyond that, Villa *et al.*[203] stated that for healthy postmenopausal women, 1 mg oral micronized estradiol supplement has a favorable effect on insulin sensitivity, whereas it shows a neutral effect on lipid metabolism, but 2 mg preparation impairs insulin sensitivity and increases TGs, despite a favorable effect on LDL-C. The therapeutic consequences of hormones are not always dosage dependent.[204]

In an *in vitro* study by Perkins *et al.*,[205] the pharmacological features of synthetic ethinylestradiol (EE), pure E2, E3, and E1 standards, as well as bioidentical estrogen (bE2 and bE3) were compared through ERs.[205] As shown by results, E2 and E3 standards have similar binding affinities to the bE2 and bE3, while E1 has a lower affinity for ERβ, and EE a higher affinity for ERα. Bhavnani *et al.*[206] also claimed that E2, E1, and ring B unsaturated estrogen interact with human ERs with different affinities. The therapeutic effects of estrogens are mediated predominantly by ERα.[207] However, ERβ and GPR30 may also play an important role in specific organs.[208,209] New pharmacological tools, such as membrane-selective SERM, have been developed to activate membrane, without activating nuclear ER, so as to enhance vascular protection without increasing the risk of breast and endometrial cancer.[210,211] The above-mentioned studies can provide ideas for the design of high-affinity binding pharmacological tools that can selectively activate either genomic or nongenomic ER signaling in target organs.

However, there is still ongoing controversy about the MHT today. The healthcare provider prescribing these medications must comprehensively review the mechanism of compounds, adverse effects, contraindications, and the potential risks before initiating therapy, to avoid exacerbating cardiovascular risk and the development of AD. Moreover, the main objective of MHT is to alleviate menopausal symptoms. Although scientific evidence suggests that MHT may positively impact energy metabolism, it is important to note that it has not yet received approval for this specific indication.[212]

Conclusion

Throughout this paper, we have systematically reviewed the critical role of estrogen *via* ERs

signaling pathway in maintaining the overall energy homeostasis of the brain and the whole body. Cessation of the ovarian function with declined circulating E2 level leads to widespread changes in glucose and lipid metabolism. The adaption of women to menopause is individualized. Initiation of MHT at an early stage of menopause may effectively enhance the metabolic rate, and attenuate the development of obesity, insulin resistance, type 2 diabetes, fatty liver, and AD. However, the MHT remains a mixed picture of benefits and risks. Thus, more studies should be conducted to further explore the underlying molecular mechanism of E2 regulation, which may reveal an innovative pharmacological target for MHT beneficial action, and provide precise guidance on the type, dosage, and route of MHT usage.

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ORCID iD
Jing Zhu https://orcid.org/0000-0002-3393-7225

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