Frontiers in Neuroendocrinology 35 (2014) 8–30

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

Estrogen: A master regulator of bioenergetic systems in the brain and body

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ARTICLE INFO

Article history:
Available online 29 August 2013

Keywords:
Adipokine
Adipose tissue
Aging
Alzheimer's disease
Biomarker
Insulin
Menopause
Metabolism
Mitochondria
Type 2 diabetes

ABSTRACT

Estrogen is a fundamental regulator of the metabolic system of the female brain and body. Within the brain, estrogen regulates glucose transport, aerobic glycolysis, and mitochondrial function to generate ATP. In the body, estrogen protects against adiposity, insulin resistance, and type II diabetes, and regulates energy intake and expenditure. During menopause, decline in circulating estrogen is coincident with decline in brain bioenergetics and shift towards a metabolically compromised phenotype. Compensatory bioenergetic adaptations, or lack thereof, to estrogen loss could determine risk of late-onset Alzheimer's disease. Estrogen coordinates brain and body metabolism, such that peripheral metabolic state can indicate bioenergetic status of the brain. By generating biomarker profiles that encompass peripheral metabolic changes occurring with menopause, individual risk profiles for decreased brain bioenergetics and cognitive decline can be created. Biomarker profiles could identify women at risk while also serving as indicators of efficacy of hormone therapy or other preventative interventions.

1. Introduction

Estrogen is a systems-level signaling molecule that regulates and coordinates multiple functions across organs, cells and genes. To achieve this integration, estrogen utilizes a repertoire of receptors and signaling pathways to activate and regulate molecular and genomic responses required for survival at the cellular, organismic and ultimately whole body level. Estrogen integration and coordination of metabolism enables the development of peripheral biomarkers which can serve as reporters of brain bioenergetics, thereby providing early detection of populations at risk for neurodegenerative diseases associated with metabolic dysfunction, such as Alzheimer's disease. Reviewed herein is estrogen action in the brain and the body with particular emphasis on estrogen regulation of metabolism, and its clinical implications. Throughout, estrogen is used to refer to 17β-estradiol (the predominant estrogen) whereas other types of estrogens are specifically identified and typically are related to formulations of hormone therapies.

2. Estrogen, estrogen receptors, and intracellular signaling pathways in the brain

Estrogens are steroid hormones primarily known for their role in promotion of female sex characteristics and reproductive capability. There are three forms of estrogens in the female body: estrone (E_1), estradiol (E_2), and estriol (E_3). During a woman's reproductive years, the principal circulating estrogen is 17β-estradiol (E_2); importantly, it is also the most potent form of estrogen. In humans, estrogens are produced by the ovaries and adrenal glands, and circulate throughout the body where they have effects on most organ systems, including brain, breast, cardiovascular (heart and

Abbreviations: 3xTgAD, triple-transgenic mouse model of Alzheimer's disease; αERKO, ERα knockout; αKGDH, α-ketoglutarate dehydrogenase; Aβ, amyloid beta$_{1-42}$, beta-amyloid; AD, Alzheimer's disease; ArKO, aromatase knockout; BMI, body-mass index; CEE, conjugated equine estrogen; CMRglu, cerebral metabolic rate of glucose uptake; COX, complex IV; CSF, cerebrospinal fluid; DPN, diarylpropionitrile (an ERβ-selective agonist); E_1, estrone; E_2, estradiol, 17β-estradiol; E_3, estriol; Estrogen, 17b-estradiol unless otherwise specified; ER, estrogen receptor; ERα, estrogen receptor alpha, also referred to as ESR1; ERβ, estrogen receptor beta, also referred to as ESR2; ERE, estrogen response element; FDG, fluorodeoxyglucose; HOMA-IR, homeostatic assessment of insulin resistance; HT, hormone therapy; IDE, insulin degrading enzyme; IGF-1, insulin growth factor-1; IGF-1R, insulin growth factor-1 receptor; IR, insulin receptor; MCI, mild cognitive impairment; mER, membrane associated estrogen receptor; MMSE, mini-mental state exam; MPA, medroxyprogesterone acetate; mtDNA, mitochondrial DNA; OVX, ovariectomized, ovariectomy; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PET, positron emission tomography; PPT, propylpyrazoletriol (an ERα-selective agonist); rCBF, regional cerebral blood flow; ROS, reactive oxygen species; SHBG, sex hormone-binding globulin; T2DM, Type II diabetes mellitus; TCA, tricarboxylic citric acid; VaD, vascular dementia.

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http://dx.doi.org/10.1016/j.yfrne.2013.08.001

vasculature), immune, reproductive (ovaries and uterus), bladder, skin, and bone (Kuiper et al., 1997).

Estrogen can cross the blood–brain barrier, and additionally, the brain can produce estrogen endogenously from cholesterol (Balthazart and Ball, 2006; Garcia-Ovejero et al., 2005; Prange-Kiel et al., 2003; Rune and Frotscher, 2005). Thus, along with its role in female physiology and reproduction, decades of research have established that estrogen is a critical signaling molecule within the brain (Brinton, 2008b). Estrogen receptors (ERs) are widely distributed in the brain, are present on both neurons and glia, and are expressed by both sexes. These receptors are highly evolutionarily conserved, with homologs in all vertebrate species. Estrogen receptors are composed of two general classes: nuclear ERs and membrane embedded/membrane associated ERs (mERs), both of which are present in the brain. There are two isoforms of classical nuclear estrogen receptors: ERα (ESR1) (HUGO Gene Nomenclature Committee, NCBI) and ERβ (ESR2) (HUGO Gene Nomenclature Committee, NCBI), which are functionally distinct and differentially distributed throughout the brain. Coding regions for both ERs are found on chromosome 6 (Menasce et al., 1993). The estrogen nuclear receptors exist initially as monomers, and dimerize prior to translocation to the nucleus, where they regulate transcription. *In vitro* evidence indicates the potential for heterodimers between ERα and ERβ (Pettersson et al., 1997), although *in vivo* evidence of this phenomenon remains to be established. In contrast to the nuclear receptors, membrane-associated estrogen receptors are monomers of ERα and ERβ. It is worth noting that in fish, a third nuclear ER has been identified, termed ERγ or ERβa (Halm et al., 2004; Hawkins and Thomas, 2004; Hawkins et al., 2000; Sabo-Attwood et al., 2004). The existence of this third ER in mammals has been investigated (Shughrue et al., 2002), and although no studies have provided concrete evidence for its presence, it would be presumptive to rule it out.

Classical estrogen signaling occurs as a result of the ER translocating to the nucleus, where it binds the estrogen response element (ERE) to regulate gene expression. Additionally, ERα can be alternatively spliced to generate three splice variants (GeneCards, ESR1), and ERβ can be alternatively spliced to generate eleven splice variants (GeneCards, ESR2). Most splice variants have been identified in breast or other cancer cell lines; because of the lack of genomic control in these cell lines, the functionality of splice variants is controversial. In brain, however, splice variants have been detected and have been associated with changes in estrogen responsivity.

2.1. Estrogen receptors alpha and beta: localization and splice variants

In rat and mouse forebrain, ERα shows a wide pattern of distribution (Brinton, 2009; Milner et al., 2001; Mitra et al., 2003; Shughrue, 2004; Shughrue et al., 1997); this is similar to the human brain, where *in situ* hybridization studies show ERα is distributed throughout the hypothalamus, forebrain, hippocampus (weakly), and amygdala (Mitra et al., 2003; Osterlund et al., 2000b; Ostlund et al., 2003). ERβ is more narrowly distributed, with high concentrations seen primarily in the hippocampus and cerebral cortex both in rodents and humans (Mitterling et al., 2010; Osterlund et al., 2000a; Ostlund et al., 2003; Shughrue et al., 1997; Shughrue and Merchenthaler, 2001). Within the hippocampus, both ERα and ERβ localize to dendritic spines, which are sites of synapse formation that show a high degree of plasticity. (Milner et al., 2005, 2001). ERα and ERβ have both been shown to mediate hippocampal-dependent learning tasks (Spencer et al., 2008); however, signaling through ERα and ERβ leads to differential expression of synaptic proteins, indicating that these two receptors have distinct roles within the hippocampus (Waters et al., 2009). In the rodent midbrain, ERβ is predominantly localized to the substantia nigra, locus coeruleus, and raphe nuclei (Mitra et al., 2003; Shughrue et al., 1997). ERα shows narrower distribution in the midbrain, and is primarily localized to the periaqueductal gray (Mitra et al., 2003; Shughrue et al., 1997). In the hindbrain and cerebellum, most ERα and ERβ immunostaining is within cell nuclei; the cerebellum shows no specific ERα staining, although it does show staining for ERβ (Mitra et al., 2003; Shughrue et al., 1997).

The effect of aging on ERα and ERβ expression and signaling is still a developing area of investigation, but a recent review thoroughly covers what is currently known (Foster, 2012). In short, data suggest that in different areas of the hippocampus, the ERα/ERβ ratio changes with age. In young and middle-aged rats, primates, and humans, ERβ is the dominant ER in the hippocampus, although ERα is present in low quantities. With aging, nuclear ERα localization increases in the dentate gyrus and CA3, but decreases in CA1 (Ishunina et al., 2007). ERα also becomes less sensitive to E_2 treatment as animals age; this is in contrast to ERβ, which shows decreased levels with age but remains responsive to E_2 treatment (Waters et al., 2011). Clinical studies have shown a linear relationship between Mini Mental State Exam (MMSE) score and ERα levels, but no relationship between MMSE and ERβ, in the frontal cortex of Alzheimer's patients (Kelly et al., 2008). The existence of variant isoforms of ERα that may influence cognitive impairment has been proposed (Kelly et al., 2008); this was later observed in a cohort of non-demented elderly (Yaffe et al., 2009). Thus the data show that decreased ERα levels and responsiveness may mediate cognitive impairment and dementia; during aging, although ERβ remains responsive to E_2, it is unable to compensate for the loss of ERα.

With aging, there is also an increase in the expression of particular ERα splice variants in the hippocampus that render much of the available ERα non-functional (Ishunina et al., 2007). Interestingly, it has been shown that elderly women are more likely than elderly men to have increased expression of ERα splice variants (Foster, 2012). ERβ splice variants are also present in the brain (Mott and Pak, 2012). A recent study proposed that one dominant negative splice variant, ERβ2, may mediate differential responses to E_2 treatment early and late after ovariectomy (OVX) in rats, such that only if estrogen treatment is initiated early after OVX is it able to prevent induction of the dominant negative ERβ2 variant (Wang et al., 2012). In addition to splice variants, there are several ERα polymorphisms that increase the risk of Alzheimer's disease (AD) specifically in women, particularly when associated with the APOE ε4 allele (Ryan et al., 2013).

2.2. Membrane-embedded estrogen receptors

In addition to the classical cytoplasmic and nuclear ERs, there are also membrane-embedded ERs, which rapidly initiate intracellular signaling pathways upon exposure to estrogen (Micevych and Dominguez, 2009; Toran-Allerand et al., 2002). These membrane sites of ER action activate both the Src/PI3K and Ras/Raf/MEKK/ERK signaling pathways, leading to activation of CREB, and they have been identified as required for E_2-inducible neuroprotection (Levin, 2001; Mannella and Brinton, 2006; Zhao et al., 2005). G protein-coupled receptors that associate with estrogen, such as G-protein coupled estrogen receptor 1 (GPER1; also called GPR30) (HUGO Gene Nomenclature Committee, NCBI), have also been identified (Maggiolini and Picard, 2010). This receptor has a high affinity for E_2, and signaling thorough it activates both cAMP/PKA and PI3K/Akt pathways (Maggiolini and Picard, 2010). 17β-estradiol binding to ERs activates signaling cascades associated with neuronal survival and function, including MAPK (Arevalo et al., 2012; Nilsen and Brinton, 2003; Singh et al., 2000), PI3K (Brinton, 2008a; Cheskis et al., 2008; Spencer-Segal et al., 2012), and PKC

(Cordey et al., 2003). Activation of both the MAPK and PI3K pathways leads to phosphorylation of CREB, which upregulates the transcription of neuronal survival genes including the anti-apoptotic protein Bcl-2 (Nilsen and Brinton, 2003; Nilsen et al., 2006; Pike, 1999; Stoltzner et al., 2001). Further, E_2 activation of the PI3K pathway has the potential to simultaneously activate the MAPK, PKC, Ca^{2+} influx and Akt signaling pathways (Mannella and Brinton, 2006; Simoncini et al., 2000), and this simultaneous activation has been shown to mediate the neuroprotective effect of E_2 (Mannella and Brinton, 2006).

Membrane-embedded ERs activate pathways that regulate calcium influx through L-type Ca^{2+} channels, which in turns activates the PI3K/Src/ERK/CREB cascade (Mannella and Brinton, 2006; Wu et al., 2005). This increases Bcl-2 expression, which potentiates the maximal mitochondrial calcium uptake capacity (Murphy et al., 1996a). The increased mitochondrial uptake of calcium induced by E_2 could thus protect neurons against the adverse consequences of excess cytoplasmic calcium. We sought to test this in a series of experiments analyzing calcium dynamics between the cytosolic and mitochondrial compartments (Nilsen and Brinton, 2003). Results showed that E_2 treatment led to increased mitochondrial sequestration of $[Ca^{2+}]^i$ when neurons were exposed to excitotoxic glutamate, which was paralleled by a decrease in cytoplasmic $[Ca^{2+}]^i$ and an increase in expression levels of Bcl-2 (Nilsen and Brinton, 2003). Importantly, despite the increased intramitochondrial calcium load, treatment with E_2 was able to preserve mitochondrial respiratory capacity (Nilsen and Brinton, 2003). In neurons derived from the aged brain, E_2 sustained calcium homeostasis comparable to the middle-aged level, and prevented transition to the dysregulation associated with aged neurons (Brewer et al., 2006).

2.3. Mitochondrial estrogen receptors

Critically, multiple laboratories have also established the presence of mitochondrial ERs (Irwin et al., 2012; Milner et al., 2005; Mitterling et al., 2010; Stirone et al., 2005; Yager and Chen, 2007; Yang et al., 2004), which emphasizes the role that estrogen plays in regulating cellular bioenergetics (Fig. 1). The mitochondrial genome contains DNA sequences that resemble half the palindromic nuclear ERE sequence (Demonacos et al., 1996). In an early experiment, ERα and ERβ were shown to directly bind mitochondrial DNA (mtDNA) *in vitro* through mitochondrial EREs, and the binding response was increased with exposure to 17β-estradiol (Chen et al., 2004). Further work has demonstrated that ERβ localizes to the mitochondria (Irwin et al., 2012; Simpkins et al., 2008). Considering the predominant location of ERβ in brain mitochondria, it is reasonable to postulate that estrogen directly modulates mitochondrial function via ERβ-mediated regulation of mtDNA transcription (Yang et al., 2004). While mechanisms by which ERs coordinate the complex signaling pathways between the membrane, mitochondria, and nucleus remain to be fully determined

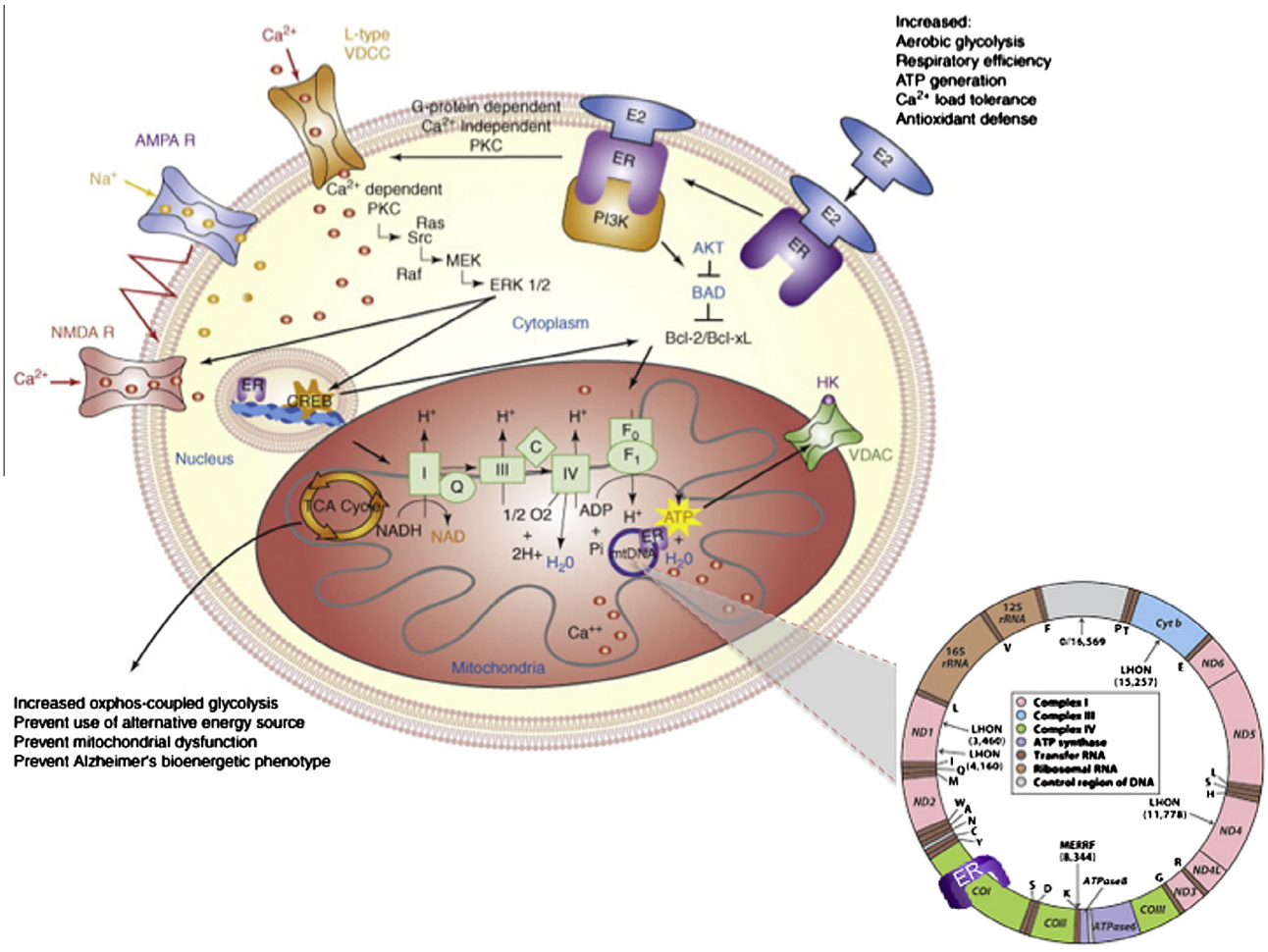

Fig. 1. Estrogen regulation of intracellular brain metabolism pathways. Estrogen-induced signaling pathways in hippocampal and cortical neurons converge upon the mitochondria to enhance glucose uptake and metabolism, aerobic glycolysis, tricarboxylic acid cycle (TCA)-coupled oxidative phosphorylation and ATP generation. In parallel, E_2 increases antioxidant defense and antiapoptotic mechanisms. Estrogen receptors at the membrane, in mitochondria, and within the nucleus are well positioned to regulate coordinated mitochondrial and nuclear gene expression required for optimal bioenergetics.

(Wagner et al., 2008), it is remarkable that ERs are perfectly positioned to coordinate events at the membrane with events in the mitochondria and nucleus (Fig. 1) (Brinton, 2008b, 2009; McEwen et al., 2001; Milner et al., 2005, 2008, 2001; Yang et al., 2004).

3. Estrogen and brain bioenergetics

The human brain, despite comprising only 2% of the body's mass, consumes 20% of the body's fuel for mitochondrial respiration and ATP generation. Thus the brain is singularly reliant on efficient mitochondrial function, and is at risk for bioenergetic decline if mitochondrial function is impaired. Estrogen has been shown to have beneficial effects on the entire bioenergetic system of the brain from glucose transport into cells to glycolysis, the tricarboxylic citric acid (TCA) cycle, oxidative phosphorylation (OXPHOS), and ATP production (Fig. 2) (Brinton, 2008b, 2009).

3.1. Estrogen regulation of glucose transport

The family of GLUT receptors mediates glucose transport into the brain. *In vivo*, glucose transporter-1 (GLUT-1) exists in two glycosylated isoforms: a 55 kD isoform that regulates glucose transport from the blood vessels into the brain, and a 45 kD isoform that regulates transport from the brain into glia. GLUT-1 is a low-affinity transporter, but is highly sensitive to changes in glucose levels. Its expression levels are closely regulated by glucose availability and demand; in particular, conditions of hypoglycemia lead to increased blood–brain barrier GLUT-1 expression (Carruthers et al., 2009; Simpson et al., 1999). Glucose transporter-3 (GLUT-3) is a high-affinity GLUT isoform that is expressed on neuronal membranes, and allows for the transport of glucose into the neuron. Glucose transporter-4 (GLUT-4) is also expressed on neuronal membranes, and is unique because its translocation from the cytoplasmic compartment to the cell membrane is regulated by insulin. Through this array of transporters, glucose enters specific cellular compartments of the brain. Thus, tracking changes in expression or function of these glucose transporters in each of the cellular compartments of the brain provides a window into understanding adaptations occurring in brain that affect both its metabolic capacity and its relationship to fuels provided from the periphery.

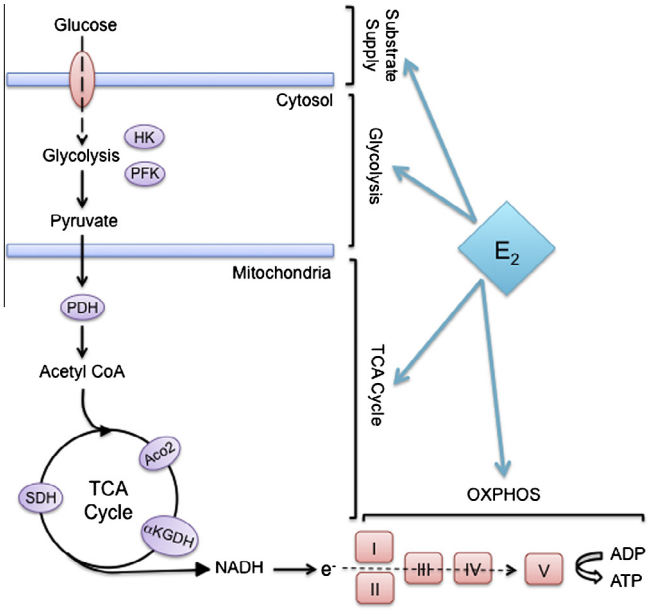

Fig. 2. Estrogen regulation of bioenergetic system. Estrogen regulates many of the key enzymes involved in mitochondrial bioenergetics, including glucose transporters, hexokinase (HK), pyruvate dehydrogenase (PDH), aconitase (Aco2), alpha ketoglutarate dehydrogenase (aKGDH), succinate dehydrogenase (SDH), and Complexes I, III, and IV of the electron transport chain.

Ovariectomy induces a significant decline in multiple glucose transporters, including GLUT-1, GLUT-3, and GLUT-4 (Cheng et al., 2001; Ding et al., 2013b; Shi and Simpkins, 1997). In both the rodent and the non-human primate, E_2 treatment prevents the OVX-induced decline in these glucose transporters (Cheng et al., 2001; Ding et al., 2012, 2013b; Shi and Simpkins, 1997). Recently, our group demonstrated that loss of ovarian hormones with reproductive aging induced a significant decline in brain glucose utilization, which could be attributed to decreased neuronal glucose transporter expression, compromised hexokinase activity, inactivation of the pyruvate dehydrogenase complex, and eventually a functionally significant decrease in mitochondrial bioenergetic function (Ding et al., 2013a).

Estrogen regulation of the insulin-sensitive glucose transporter is particularly interesting, as it requires a simultaneous increase in levels of E_2/ER and the insulin/insulin receptor (IR) system. In the rodent brain, coupling between estrogen and insulin involves insulin's rodent brain homolog insulin growth factor-1 (IGF-1) and its receptor (IGF-1R). The synergistic coupling between ERs and IGF-1R has been extensively investigated (Arevalo et al., 2012; Cardona-Gomez et al., 2002; Garcia-Segura et al., 2010, 2000; Mendez and Garcia-Segura, 2006; Mendez et al., 2006). IGF-1R and ERα can form a macromolecular complex to enable downstream signaling functions, such as activation of the PI3K signaling pathway that leads to phosphorylation and activation of Akt (Garcia-Segura et al., 2010; Mendez et al., 2006). The phosphorylated (active) form of Akt has been shown to selectively co-localize with GLUT-4 in IGF-1-expressing neurons, leading to an increase in glucose transport through this regulation of GLUT-4 (Cheng et al., 2000). In the ovariectomized primate referenced above, it was noted that IGF-1R mRNA is concentrated in neurons in a similar distribution to GLUT-3 and -4 (Cheng et al., 2001). The interaction between ER and IGF-1 provides compelling evidence for the coordinated roles of IGF-1, the PI3K to Akt signaling pathway, and ER signaling in estrogen-inducible promotion of neuronal metabolism and neuroprotection.

Interestingly, the above *in vitro* and *in vivo* studies correspond well with what has been observed in humans. In patients with AD, low insulin levels, decreased expression of insulin receptors and attenuated insulin signaling are detected in brain regions vulnerable to AD pathology, particularly the hippocampus (Schioth et al., 2012). It is reasonable to hypothesize that attenuated insulin signaling could at least partially account for the memory impairment seen early in the course of the disease. Alleviation of insulin deficits by intranasal insulin administration was found improve cognitive function in preclinical animal models, healthy controls, and patients with Alzheimer's disease (Benedict et al., 2011). Further analyses suggest that insulin effects can be modified by both sex and APOE genotype, as well as by insulin dose (Claxton et al., 2013).

Soluble amyloid oligomers have been shown to disrupt insulin signaling by causing a loss of insulin receptors (Zhao et al., 2008). In rodents, elevated brain amyloid beta$_{1-42}$ (Aβ) levels were associated with low circulating IGF-1, whereas increasing serum IGF-1 reduced Aβ burden (Carro et al., 2002). In female rats, IGF-1 gene expression was consistently decreased following both ovariectomy and reproductive senescence (Mao et al., 2012; Zhao et al., 2012). This was paralleled by increased expression of genes involved in Aβ generation. In addition to its role in promoting insulin/IGF-1 function, estrogen further promotes Aβ degradation and clearance by upregulating insulin-degrading enzyme (IDE) and neprilysin gene and protein expression (Jayaraman et al., 2012; Zhao et al., 2011b).

3.2. Estrogen regulation of glycolysis

In addition to facilitating glucose transport, estrogen also promotes neuronal aerobic glycolysis. In rodents, E_2 increases activity of the glycolytic enzymes hexokinase (soluble and membrane-bound), phosphofructokinase and pyruvate kinase within 4h of exposure (Kostanyan and Nazaryan, 1992). Hexokinases are critical enzymes, because they bind the voltage-dependent anion channel (VDAC) on the mitochondrial outer membrane in order to link mitochondrial ATP synthesis to glucose metabolism (Gottlob et al., 2001). This coupling is regulated by Akt, which associates with hexokinase II (HKII) (Miyamoto et al., 2008); HKII activity is then required for the antiapoptotic effect of Akt (Gottlob et al., 2001). E_2 acts on this system from multiple angles, both through activating Akt (Mannella and Brinton, 2006; Singh, 2001; Znamensky et al., 2003) and through increasing HKII activity (Kostanyan and Nazaryan, 1992), and thus it is hypothesized that estrogen may play a role in promoting the association of HKII and VDAC in neurons.

3.3. Estrogen regulation of mitochondrial energy production

A substantial number of the signaling pathways regulated by estrogen converge upon mitochondria (Brinton, 2008a; Mannella and Brinton, 2006; Nilsen and Brinton, 2003, 2004; Nilsen et al., 2006), and the upregulation of glucose transport and glycolysis mediated by estrogen is complemented by its potentiation of mitochondrial bioenergetics. Using proteomic analysis of brain mitochondria from female rats treated with E_2, our lab identified several metabolic enzymes whose activity and protein expression levels were regulated by E_2, including pyruvate dehydrogenase (PDH), aconitase, and ATP synthase (Nilsen et al., 2007). E_2 treatment increased the expression of several PDH subunits (Nilsen et al., 2007), which is important because PDH is the primary regulatory enzyme that links glycolysis to the TCA cycle through the generation of acetyl CoA. Further, in the brain PDH is responsible for directing acetyl-CoA either to the TCA cycle or to be used for acetylcholine synthesis (Holmquist et al., 2007). E_2 treatment increased expression of the Complex I β subunit 8 (Irwin et al., 2012). E_2 also increased activity (Nilsen et al., 2007; Yao et al., 2012) and expression (Nilsen et al., 2007) of Complex IV (COX), which is consistent with previous findings (Bettini and Maggi, 1992; Stirone et al., 2005). Lastly, E_2 treatment led to increased expression of Complex V/ATP synthase F_1 subunits α and β (Nilsen et al., 2007). We had previously reported estrogen-induced increases in ATP levels in primary neuronal cultures (Brinton et al., 2000), which coalesces well with results seen in the proteomic analysis. Maximal mitochondrial respiratory rate in neurons and glia was also increased by E_2 treatment, and E_2 treatment protected against electron transport chain inhibitors (Yao et al., 2012). Thus the results of our analyses show that estrogen produces a coordinated response of many mitochondrial enzymes, leading to optimal glucose metabolism in the brain.

Further studies in our laboratory investigated the contributions of each of the estrogen receptor isoforms, ERα and ERβ, to the promotion of mitochondrial bioenergetics (Irwin et al., 2012). Using the ERα-selective agonist propylpyrazoletriol (PPT), which is 410-fold more selective for ERα than ERβ (Stauffer et al., 2000), and the ERβ-selective agonist diarylpropionitrile (DPN) is 70-fold more selective for ERβ than ERα (Meyers et al., 2001), Irwin *et al* were able to probe the effects of signaling cascades activated through ERα and ERβ. Hippocampal mitochondrial enzymes that showed increases in protein expression levels after treatment with PPT included PDH subunit E1 and ATP synthase F_1 subunit α. DPN upregulated expression levels of COX subunit I, which is mtDNA-encoded. As PPT had no effect on COX subunit I expression, this suggests that mtDNA transcription is regulated by ERβ-dependent mechanisms. COX subunit IV expression and activity were upregulated by both PPT and DPN. This subunit is encoded by nuclear DNA, which suggests that ERα and ERβ are independently capable of upregulating specific mitochondrial proteins. Both agonists also reduced mitochondrial lipid peroxides, consistent with previous findings of estrogen induction of the antioxidants peroxiredoxin 5 and manganese superoxide dismutase (MnSOD) (Nilsen et al., 2007; Yao et al., 2012). Assessment of mitochondrial respiration from the same samples indicated that both PPT and DPN independently regulate mitochondrial function, often with comparable results, leading to enhanced mitochondrial respiration (Irwin et al., 2012). Consistent with the ERβ activation of mitochondrial function, analyses of an ERβ-selective formulation, PhytoSERMS, showed that the formulation induced a significant rise in mitochondrial respiration (Yao et al., 2013; Zhao et al., 2011a). While both ERα and ERβ promote mitochondrial function, targeting ERβ generally results in greater efficacy of mitochondrial respiration (Irwin et al., 2012; Yao et al., 2013).

Estrogen action at the mitochondria extends to protection against Aβ. Estrogen treatment not only increases ATP production in healthy hippocampal neurons, but also sustained ATP generation after the neurons were exposed to Aβ (Brinton et al., 2000). Ovariectomy in mice leads to both a decline in mitochondrial bioenergetics and an elevation in mitochondrial Aβ, but if estrogen treatment is started immediately following ovariectomy, both of these deleterious events are prevented (Yao et al., 2012).

3.4. Estrogen regulation of oxidative stress

A byproduct of oxidative phosphorylation is the production of reactive oxygen species (ROS). During normal (non-pathological) oxidative phosphorylation, mitochondria generate 1–4% incompletely reduced oxygen which can react to form ROS (Cecarini et al., 2007; Sugioka et al., 1988). Electron transport chain complexes I and III have been implicated as the primary sources of ROS (Cadenas and Davies, 2000). Thus, a deficit in complex IV activity without a corresponding decline in activity of complexes I and III – as described in AD patients in Section 4 – could lead to increased ROS leak (Atamna and Frey, 2007). Because mitochondria are the main source of ROS production, they also suffer the greatest oxidative stress when excess ROS are produced. Many components of the mitochondrial bioenergetic network are particularly vulnerable to oxidative stress, e.g., lipid peroxidation of mitochondrial membranes and protein damage on the electron transport chain, which increases the risk of severe mitochondrial impairment that can lead to energetic failure of the cell and/or apoptosis (Blass, 2000; Lin and Beal, 2006; Yao et al., 2004).

In vitro, estrogen has been shown to protect against DNA damage induced by hydrogen peroxide (H_2O_2) and arachidonic acid (Moor et al., 2004; Tang and Subbiah, 1996). Estrogen also increases expression of several antioxidant enzymes, including peroxiredoxin 5, glutaredoxin and MnSOD (Nilsen and Brinton, 2004; Nilsen et al., 2007). In rodents, ovariectomy led to an increase in lipid peroxides that was prevented by E_2 treatment (Irwin et al., 2008; Yao et al., 2012). Estrogen-induced rise in antioxidants and associated reduction in free radicals, and lower oxidative damage to mitochondrial DNA, has been proposed as a mechanism to explain the greater longevity of females relative to males (Borras et al., 2007; Vina et al., 2005, 2006).

4. Mitochondrial relevance to Alzheimer's disease

Mitochondria play a critical role in generating energy for the cell, and increasing evidence links mitochondrial dysfunction to

age-associated neurodegenerative disorders such as Alzheimer's disease (Brinton, 2008a; Moreira et al., 2006, 2010; Mosconi et al., 2011, 2009a; Swerdlow and Khan, 2009). Deficits in the activity of several key enzymes involved in mitochondrial energy generation have been described in AD. Decreased PDH activity in post-mortem brain homogenate from AD patients was one of the first deficits described (Perry et al., 1980), and this has since been confirmed by a number of other groups (Sheu et al., 1985; Sorbi et al., 1983; Yates et al., 1990). Microarray analyses also show a downregulation of PDH gene expression in patients with incipient AD, providing further support that a deficit in PDH activity is an early event in AD pathogenesis (Blalock et al., 2004). Activity of α-ketoglutarate dehydrogenase (αKGDH), the rate-limiting enzyme of the TCA cycle, is also deficient in post-mortem brain tissue from patients with AD (Butterworth and Besnard, 1990; Gibson et al., 2000b, 1988; Mastrogiacoma et al., 1996, 1993). A decline in αKGDH activity is positively correlated with clinical dementia in sporadic (non-genetic) forms of AD, but patients who are APOE ε4 carriers (Gibson et al., 2000a) or carry the Swedish AβPP mutation KM670/671NL (Gibson et al., 1998) show the most reliable correlation between decreased αKGDH activity and degree of dementia. The most consistently documented deficit in mitochondrial enzyme function is decreased activity of COX, the penultimate complex of the electron transport chain. Deficient COX activity has been identified in post-mortem brain tissue (Cottrell et al., 2001; Kish et al., 1992; Maurer et al., 2000; Mutisya et al., 1994; Parker et al., 1994b) as well as platelets (Bosetti et al., 2002; Cardoso et al., 2004; Parker et al., 1990, 1994a; Valla et al., 2006a) and fibroblasts (Curti et al., 1997) from AD patients. As further evidence that a mitochondrial deficit is an early event in AD pathogenesis, the reduction of COX activity has been identified in peripheral tissues from patients with mild cognitive impairment (MCI) (Swerdlow and Kish, 2002; Valla et al., 2006a). Additionally, young adult APOE ε4 carriers without overt AD pathology showed lower COX activity in the posterior cingulate than young adult non-carriers (Valla et al., 2010). Considering that this deficit in COX activity is seen in peripheral tissues and not just in brain, it is unlikely to be a result of neurodegeneration (Swerdlow, 2009). Indeed, the fact that COX deficiency is not restricted to the brain suggests a systemic aspect to AD (Maruszak and Zekanowski, 2011; Swerdlow, 2011).

In the "cybrid model" of AD, neural cultures that lack endogenous DNA (termed ρ0 cells) are fused with platelets that lack a nucleus, creating "cybrids" (Swerdlow et al., 1997). Interestingly, when the cells are fused with platelets from AD patients, they exhibit characteristics that match the findings from clinical AD specimens, including decreased COX function that can be passed down through the cybrid lines (Swerdlow, 2007). This provides evidence that mitochondria from AD patients have particular abnormalities that are carried within mtDNA and are thus heritable, and which may explain the enzyme complex deficiencies seen in individuals with AD.

Multiple *in vitro* and *in vivo* preclinical analyses have demonstrated a decline in mitochondrial function prior to the onset of Alzheimer's histopathological features. Results of these analyses indicate decreased metabolic enzyme expression and activity, decreased cerebral glucose metabolism, increased oxidative stress, and increased mitochondrial Aβ load (Chou et al., 2011; Du et al., 2010; Hauptmann et al., 2009; Nicholson et al., 2010; Silva et al., 2011; Yao et al., 2009). Thus this decline in brain mitochondrial function may serve as a biomarker of AD risk as well as a therapeutic target.

An impairment of mitochondrial bioenergetics and oxidative phosphorylation is often closely associated with increased free radical production and subsequent oxidative damage. As mentioned above in Section 3.4, the consistently documented deficit in complex IV activity which occurs without a corresponding decline in activity of complexes I and III could clog the electron transport chain and lead to increased ROS leak (Atamna and Frey, 2007). Animal models of AD show increased free radical generation and oxidative damage to cellular components prior to the development of pathology (Nunomura et al., 2009; Pratico et al., 2001; Rhein et al., 2009; Wang et al., 2005; Yao et al., 2009). Further, post-mortem analysis of brains from Alzheimer's patients show markers of increased oxidative stress, including lipid peroxides, 8-oxoguanine, and oxidized amino acids (Gibson and Shi, 2010; Nunomura et al., 2009; Reddy, 2006). Interestingly, an increase in oxidative stress has been demonstrated to increase β-amyloid production *in vitro* and *in vivo* (Moreira et al., 2007; Nunomura et al., 2001).

Increasing evidence indicates that mitochondria are direct targets of Aβ. Aβ has been shown to accumulate inside mitochondria, where it interacts with the mitochondrial protein Aβ-binding-alcohol-dehydrogenase (ABAD), resulting in decreased COX activity and increased oxidative stress (Lustbader et al., 2004; Reddy and Beal, 2008; Takuma et al., 2005). In AD cybrids, Aβ-induced toxicity is exacerbated in parallel with mitochondrial dysfunction (Cardoso et al., 2004). At the same time that Aβ exerts its toxicity upon the mitochondria, compromised mitochondrial function – in particular, a decline in mitochondrial bioenergetics and increased levels of ROS – further drives the degenerative process by increasing Aβproduction. The end result is a vicious cycle in which excessive Aβ accumulation and sustained mitochondrial dysfunction synergistically exacerbate each other, leading to activation of a multitude of neurodegenerative pathways (Cardoso et al., 2004; Silva et al., 2011; Swerdlow et al., 2010; Yao et al., 2011).

5. Estrogen regulation of whole-body metabolism

In addition to the brain, estrogen activates signaling pathways in nearly every tissue of the body; hence these pathways would be affected by loss of ovarian hormones associated with surgical or natural menopause (Fig. 3). Menopause is associated with a significant decline in the ovarian production of both 17β-estradiol, the predominant estrogen during a woman's reproductive years, and progesterone (Brinton, 2010; Nejat and Chervenak, 2010; Soules et al., 2001). Clinically, menopause is defined by one year of amenorrhea following the final menstrual period. Perimenopause typically begins approximately 2 years before menopause, and it encompasses the early and late transition stages as well as the first year after clinically-defined menopause (Soules et al., 2001). This perimenopausal transition is characterized by widely fluctuating hormone levels (Soules et al., 2001). In most women, the menopausal transition takes about 4 to 5 years (Woods and Mitchell, 2004), with the average age of menopause at 51 years (ESHRE Capri Workshop Group Authors, 2011). After menopause, estradiol levels no longer fluctuate as they did during perimenopause; instead, the ovaries gradually produce declining levels of estradiol and estrone becomes the predominant circulating estrogen (Nejat and Chervenak, 2010). The dysregulation of ovarian hormone secretion characteristic of the menopausal transition is in contrast to the male andropause, in which testosterone levels decrease steadily over a number of years (Ferrari et al., 2013).

5.1. Estrogen, adiposity, and obesity

Adiposity is a measure of the amount of adipose tissue (fat deposition) in the body. Adipose tissue is preferentially stored in the form of subcutaneous adipocytes, but if energy intake is too high, the body will store fat as intra-abdominal visceral adipose tissue. This visceral fat is associated with most of the health risks of adiposity (Jensen, 2008). As adiposity increases, an individual's risk of developing insulin resistance, diabetes, hypertension, and

	Age (Both Genders)	Menopause	Hormone Therapy	Alzheimer's Disease
Adipose Tissue	Increases	Re-distribution of adipose tissue to visceral fat stores	Lesser accumulation of weight, fat mass, and/or centrally located fat mass	Obesity, especially in middle age, increases AD risk
Obesity	Increased risk	Increased risk due to increased adipose tissue		
Insulin Resistance	Increased risk	Increased risk due to increased visceral adipose tissue	Beneficial effects depending on formulation	Insulin resistance increases AD risk
Type 2 Diabetes	Increased risk	Distinct increase in risk at menopause	HT decreases incidence of T2DM	T2DM increases AD risk
Leptin	Circulating levels are proportional to amount of adipose tissue	Women have higher levels than men; no direct effect of menopause	HT may promote healthy leptin levels	Lower leptin levels associated with increased risk for AD
Ghrelin	Age-related decline	Menopause effect unknown; *in vivo* studies suggest ghrelin levels increase after menopause	HT effect may differ based on metabolic status	No strong effect of ghrelin levels on AD risk
Adiponectin	Age-related increase	No direct effect of menopause; any change secondary to obesity/IR	Unclear; different effects with different HT formulations	Higher adiponectin levels associated with increased risk for AD
Sex Hormone Binding Globulin	Circulating levels are inverse to insulin levels	No direct effect; levels may change due to adiposity	Beneficial effects depending on formulation	Higher SHBG associated with cognitive decline and AD risk

Negative metabolic effects of menopause are primarily driven by dysregulation of ER signaling in adipose tissue

Fig. 3. Estrogen regulation of whole-body metabolism. Estrogen receptors are expressed throughout peripheral systems involved in metabolism. Estrogen affects adipose tissue distribution and risk of obesity, insulin resistance and risk of diabetes, and concentration of the adipokines leptin, ghrelin, and adiponectin. Loss of estrogen at menopause leads to significant changes in many of these systems, which can be stabilized with the use of hormone therapy. Adverse metabolic profiles, e.g. type 2 diabetes and metabolic syndrome, can increase risk of developing Alzheimer's disease.

cardiovascular disease also increases (Pi-Sunyer, 2002; Poirier et al., 2006). Specifically, intra-abdominal obesity is associated with the greatest risk of all of these diseases independent of total body adiposity (Despres, 1993; Pouliot et al., 1992).

Adipose tissue has a different pattern of distribution in men and women. Age-matched men tend to accumulate a greater amount of abdominal fat relative to premenopausal women, who accumulate fat in a metabolically healthier gluteo-femoral pattern that is promoted by estrogen (Carr, 2003; Krotkiewski et al., 1983). After menopause, when estrogen levels drop, women experience a general increase in weight (Davis et al., 2012a; Pimenta et al., 2013) as well as a redistribution of adipose tissue leading to increased abdominal fat deposition (Bjorkelund et al., 1996; Toth et al., 2000; Zamboni et al., 1992). Importantly, the increased abdominal fat in postmenopausal women tends to be visceral and not subcutaneous fat (Lovejoy et al., 2008). This effect is also seen in healthy pre-menopausal women treated with gonadotropin-releasing hormone (GnRH) agonists (Revilla et al., 1998; Yamasaki et al., 2001). Thus men have an unhealthier adiposity profile compared to women before menopause, but after menopause the prevalence of intra-abdominal adiposity rises significantly in women.

Estrogen receptors are present in adipose tissue, indicative of the potential for estrogen regulation of adipocyte function (Mayes and Watson, 2004; Pallottini et al., 2008; Pedersen et al., 1996). ERα and ERβ may differentially mediate estrogen's effects on adipose tissue, with ERα predominantly regulating adipose homeostasis via growth and proliferation of adipocytes, and ERβ regulating sex-specific distribution of adipose tissue (Pallottini et al., 2008). Estrogen signaling pathways mediated through ERα have been shown to upregulate α2A-adrenergic receptor expression in subcutaneous but not visceral adipose tissue (Pedersen et al., 2004). The α2A-adrenergic receptor controls anti-lipolytic pathways, promoting the accumulation of adipose tissue. Thus E_2 signaling can bias adipose distribution towards the "healthier" subcutaneous fat depots vs. unhealthy visceral fat deposition (Pallottini et al., 2008). Differential ERα and ERβ effects on adiposity have been investigated using ERα knockout (αERKO) mice, which develop severe intra-abdominal obesity (Heine et al., 2000). This provides evidence that ERα positively regulates adipose homeostasis and metabolism, whereas in the absence of ERα, unregulated signaling through ERβ promotes an unhealthy adipose phenotype (Naaz et al., 2002).

Sex dimorphisms in the distribution of ERα and ERβ in adipose tissue have been reported. Mature human adipocytes express both ERα and ERβ mRNA; expression of ERα is identical between the sexes whereas mRNA levels of ERβ are higher in women (Dieudonne et al., 2004). In human adipocytes isolated from subcutaneous and visceral fat depots from men and premenopausal women, exposure to E_2 resulted in upregulated ERα mRNA levels in both adipocyte types in men, but only subcutaneous adipocytes in women. In men, E_2 exposure did not affect ERβ mRNA levels, but in women ERβ mRNA was upregulated – again, only in subcutaneous adipocytes (Dieudonne et al., 2004). This suggests that men are more predisposed towards ERα-dominant adipose regulation, whereas women have a more balanced ratio of ERα and ERβ adipose regulation before menopause, which could explain sex-specific patterns of adipose tissue distribution. After menopause, however, a shift in the ERα/ERβ ratio towards greater ERβ signaling could mediate the postmenopausal increase in weight (Tomicek et al., 2011).

The issue of postmenopausal hormone therapy (HT) and changes in weight has been the subject of controversy. A meta-

analysis published in 2000 indicated no difference in postmenopausal weight gain between women taking and not taking HT, but had insufficient data to assess HT effects on body-mass index (BMI), waist-hip ratio, or fat mass (Norman et al., 2000). However, a more recent meta-analysis conducted by the Endocrine Society reported that HT was associated with less accumulation of weight, fat mass, and/or centrally located fat mass (Santen et al., 2010). The 2000 meta-analysis was potentially influenced by its use of the term "weight"; at menopause, there are large changes in both the distribution of body fat and the proportions of fat to non-fat mass, all of which can affect weight in different ways (Santen et al., 2010). Because increases in adiposity can be subcutaneous or visceral, women may experience a gain in weight, but their overall adipose profile could be healthier. Consistent with this postulate, HT use is associated with decreased abdominal/visceral fat (Haarbo et al., 1991; Salpeter et al., 2006). Additionally, it may be that some types of HT lead to greater weight gain than others (O'Sullivan et al., 1998), and weight changes may be less predictable in already obese women (Santen et al., 2010). Overall, in non-overweight and non-obese women, results from the Endocrine Society meta-analysis indicate that postmenopausal HT protects against weight gain, and also promotes less adipose tissue deposition in visceral fat stores (Santen et al., 2010).

Adiposity exists along a continuum, and a high degree of adiposity is referred to as obesity. Recent prevalence estimates show that approximately 70% of men and 62% of women in the US are either overweight (BMI > 25) or obese (BMI > 30); although rates of obesity are comparable between the sexes, more women fall into the category of extreme obesity (BMI > 40) (Ogden et al., 2006). This is a critical problem because obesity, specifically visceral obesity, is correlated with a large number of adverse cardiovascular outcomes. It is an established risk factor for coronary heart disease, which explains why premenopausal women have a lower risk of heart disease than age-matched men, but an increased risk after menopause (ESHRE Capri Workshop Group Authors, 2011; ESHRE Capri Workshop Group, 2006). Obesity is also well recognized as the primary risk factor for both insulin resistance (a pre-diabetic condition) and type 2 diabetes (Ahima, 2009; Pi-Sunyer, 2002).

Outcomes of multiple studies demonstrate that obesity is associated with an increased risk of dementia, including late onset AD. Increased BMI in middle-aged populations (Kivipelto et al., 2005; Whitmer et al., 2008, 2005) and older populations (Gustafson et al., 2003) is predictive of higher risk of all forms of dementia. In the Baltimore Longitudinal Study of Aging, both men and women showed associations between mid-life increases in BMI and higher incidence of AD (Beydoun et al., 2008). Measurements of waist to hip ratio in middle-aged and younger elderly individuals have also been shown to robustly correlate with higher risk of late-onset AD (Luchsinger et al., 2011a,a). There are some reports of no association between BMI and AD risk (Stewart et al., 2005) or of low BMI being related to AD risk (Nourhashemi et al., 2003); however, those results are likely affected by the age group being studied. Most research indicates that elevated BMI in middle age is related to an increased risk of dementia, while such association diminishes in elderly populations (Fitzpatrick et al., 2009; Luchsinger, 2008).

5.2. Estrogen and insulin resistance

Insulin is pivotal to maintaining and sustaining glucose metabolism in the periphery and in the brain (Cholerton et al., 2011; Craft, 2007; De La Monte, 2012). Insulin resistance is a state in which the tissues that require blood glucose have a diminished response to insulin, and the subsequent reduced clearance of glucose from blood feeds back onto the pancreas to increase secretion of insulin to induce glucose uptake (Luchsinger, 2008). Insulin resistance is primarily caused by obesity, particularly visceral obesity (Luchsinger et al., 2011b). Susceptibility to developing insulin resistance is known to increase with age (Carr, 2003; Iozzo et al., 1999), but there is less evidence that sex differentially affects development of insulin resistance. Fasting insulin (Poehlman et al., 1995; Razay et al., 2007) and glucose (Dallongeville et al., 1995; Lynch et al., 2002) levels have been shown to rise as estrogen levels decrease during the menopausal transition, but this is proposed as a secondary response to the change in body fat distribution and not a direct effect of estrogen decline (Wing et al., 1992, 1991). One study suggests women may have differential insulin metabolism after menopause, with postmenopausal women producing less insulin, but eliminating it more slowly (Walton et al., 1993).

The effects of estrogen signaling through ERs on insulin production have been studied *in vivo* using aromatase knockout mice (ArKO), which lack the enzyme responsible for conversion of androgens to estrogens (Jones et al., 2000). These animals develop insulin resistance by one year of age; as in humans, this is likely due to increased visceral fat. Larger fat depots lead to greater release of free fatty acids, which has the potential to disturb insulin dynamics in the liver (Pallottini et al., 2008). A similar development of insulin resistance in conjunction with an increase in fat mass is seen in ERα knockout (αERKO) mice (Bryzgalova et al., 2006; Heine et al., 2000; Manrique et al., 2012). Ovariectomy provides a good model of postmenopausal insulin resistance: loss of ovarian hormones induces an increase in body weight along with increased plasma glucose levels and decreased plasma insulin response to glucose, and this can be reversed through treatment with estrogen after ovariectomy (Bailey and Ahmed-Sorour, 1980; Ding et al., 2012; Zhu et al., 2013). Still, in these models, the challenge remains to distinguish between primary insulin resistance mediated by loss of estrogen and insulin resistance that develops secondary to adipose deposition.

In human clinical research, the majority of studies have focused on the impact of hormone therapy on incidence of type 2 diabetes (T2DM) as opposed to insulin resistance, although several studies have investigated the effect of HT on insulin resistance. A meta-analysis of studies of HT and insulin resistance indicated that postmenopausal HT significantly reduced levels of insulin resistance (as measured by the homeostatic assessment of insulin resistance (HOMA-IR) score) (Salpeter et al., 2006). Interestingly, two studies in non-human primates found that specific hormone formulations may change estrogen's beneficial effects on insulin resistance; in these primates, a conjugated equine estrogen (CEE) formulation decreased body mass and HOMA-IR, whereas addition of the progestin medroxyprogesterone acetate (MPA) significantly increased body weight, fat mass, and HOMA-IR (Shadoan et al., 2003, 2007).

Insulin can cross the blood–brain barrier (Park, 2001) and insulin receptors are expressed throughout the brain with particularly high receptor densities in the hippocampus and entorhinal cortex (Burns et al., 2011). Insulin resistance in non-diabetic (or pre-diabetic) individuals is associated with increased risk of cognitive impairment and dementia (Craft, 2005; Xu et al., 2007; Yaffe et al., 2004). Further, hyperinsulinemia as a response to insulin resistance has been associated with increased risk of AD in multiple cross-sectional and longitudinal studies (Kuusisto et al., 1997; Luchsinger et al., 2004; Peila et al., 2004; Razay and Wilcock, 1994; Stolk et al., 1997). In a recent study, hyperinsulinemia a decade or more before death correlated with presence and severity of amyloid plaques upon autopsy (Matsuzaki et al., 2010). Additionally, HOMA-IR negatively correlates with hippocampal volume in cognitively normal middle-aged women (Rasgon et al., 2011). Within the brain, insulin may lead to decreased clearance of Aβ by competing for the insulin-degrading enzyme (Farris et al., 2003).

Insulin has also been shown to increase tau phosphorylation (Park, 2001).

Early preclinical analyses indicated that a decreased cerebral metabolic rate of glucose uptake (CMRglu) is evident in rodent models of diabetes (Garris et al., 1984; Vannucci et al., 1997). These findings have also been shown in humans: higher insulin resistance was associated with decreased CMRglu in the same regions that show hypometabolism in AD (Baker et al., 2011). This was replicated in a later study in which higher fasting glucose in non-diabetic individuals was associated with decreased CMRglu in AD-affected brain regions (Burns et al., 2013). These findings support earlier analyses in humans indicating that a decrease in the cerebral metabolic rate of glucose uptake is one of the earliest events in the pathogenesis of AD (Mosconi et al., 2006; Reiman et al., 1996b). Collectively, preclinical and clinical data provide evidence of a link between development of insulin resistance and increased risk of AD, and suggest that insulin resistance could be a biomarker of risk of AD or preclinical AD.

5.3. Estrogen and diabetes

The association between ovarian hormone loss and development of dysregulation of glucose homeostasis dates back decades. In preclinical analyses, ovariectomy resulted in increased plasma glucose levels, which was prevented by estrogen treatment (Bailey and Ahmed-Sorour, 1980; El Seifi et al., 1981). Estrogen regulation of insulin and glucose homeostasis is mediated through ERα receptors, which – in addition to their expression pattern in adipose tissue –are also expressed in the liver, pancreatic beta cells, and skeletal muscle (Meyer et al., 2011; Sutter-Dub, 2002). This allows for coordination of signals regulating metabolic homeostasis in response to hormonal milieu. ERα in pancreatic beta cells has been proposed to regulate insulin production *in vivo*, such that it has an anti-diabetic effect (Le May et al., 2006; Wong et al., 2010). Consistent with these findings, αERKO mice show impaired glucose tolerance and increased insulin resistance (Ribas et al., 2010). Several studies indicate a key role of mERs in regulating pancreatic beta cell function (Nadal et al., 2004; Sutter-Dub, 2002). Collectively, preclinical analyses indicate a role for estrogen in sustaining insulin and glucose homeostasis that underlies a healthy metabolic profile.

However, the relationship between estrogen levels and diabetes following menopause is complicated. Several studies have shown that, in women, higher endogenous estrogen levels after menopause are associated with greater risk of developing insulin resistance and diabetes (Ding et al., 2007; Kalish et al., 2003; Oh et al., 2002). An increase in diabetes risk factors was also seen in early studies using high-estrogen HT (Wynn et al., 1979; Wynn and Doar, 1966). However, the Women's Health Initiative (WHI) (Margolis et al., 2004), Heart and Estrogen/Progestin Replacement Study (Kanaya et al., 2003) and the Nurses' Health Study (Manson et al., 1992) all reported that women taking HT had fewer cases of incident diabetes. It should be noted that most of these large epidemiological studies used combination hormone therapy (CEE + MPA), so it is also unclear how well the results generalize to other HT regimens. Several recent prospective cohort studies have also found reduced incidence of new-onset diabetes in women taking HT (de Lauzon-Guillain et al., 2009; Pentti et al., 2009); this effect was much stronger for women taking oral HT vs. transdermal HT (de Lauzon-Guillain et al., 2009) and for women who had long-term HT exposure (Pentti et al., 2009). In the WHI trial, women with larger waist circumference measurements showed a greater beneficial effect of HT on decreasing diabetes risk (Margolis et al., 2004). An unresolved issue is whether HT has a direct effect on diabetes risk through regulation of pancreatic ERα signaling, or an indirect effect through decreasing obesity.

Better concordance exists between outcomes of preclinical and clinical analyses of dysregulated glucose metabolism and cognitive function. Diabetes is strongly linked to cognitive impairment in both preclinical and clinical studies. Rats with streptozotocin-induced diabetes have deficits in learning and memory (Baydas et al., 2003; Kucukatay et al., 2007; Lupien et al., 2003; Stranahan et al., 2008; Tiwari et al., 2009; Ye et al., 2011). Both pigs and rats with combined diabetes and hypercholesterolemia show increased blood–brain barrier permeability and increased Aβ plaque deposition (Acharya et al., 2013). Diabetic animal models also show decreased insulin uptake into the brain and consequent reduced levels of neuronal insulin (Banks et al., 1997; Baskin et al., 1985; Kaiyala et al., 2000).

Persons with diabetes have a high risk of cognitive dysfunction, including amnestic MCI (Luchsinger et al., 2007b; Solfrizzi et al., 2004) and all types of dementia (Brayne et al., 1998; Brismar et al., 2007; Northam et al., 2006; Ott et al., 1999; Ristow, 2004; Stewart and Liolitsa, 1999). One study reported that diabetes was only related to risk of vascular dementia (VaD) (MacKnight et al., 2002), whereas others have reported that diabetes is associated with increased risk of developing both AD and VaD, but that the relative risk for VaD is greater than that for AD (Luchsinger et al., 2005, 2001; Yoshitake et al., 1995). However, the majority of studies have found diabetes to be related to a higher risk of AD, particularly late-onset AD (Arvanitakis et al., 2004; Cheng et al., 2011; Leibson et al., 1997; Luchsinger et al., 2005; Peila et al., 2002). Two recent meta-analyses identified 15 separate studies in which the association between AD and diabetes was investigated, and concluded that diabetes is an independent risk factor for AD (Vagelatos and Eslick, 2013; Williams et al., 2010). The presence of diabetes in patients who are newly diagnosed with AD is also related to greater baseline cognitive impairment and more rapid progression of AD (Sanz et al., 2012).

The clear association between type 2 diabetes and risk of dementia emphasizes the importance of strategies that reduce the risk of developing insulin resistance and dysregulation of glucose homeostasis in both the periphery and the brain. Thus, clearly establishing the factors that determine efficacy of estrogen or hormone therapy to reduce the risk of type 2 diabetes has the potential to greatly impact both the incidence of both type 2 diabetes and associated dementias.

5.4. Estrogen and leptin

Leptin is an adipokine secreted by adipose tissue that has a strong effect on regulating energy intake and expenditure (Brennan and Mantzoros, 2006). Circulating levels of leptin are directly proportional to the amount of adipose tissue in the body. Leptin functions through binding leptin receptors in the hypothalamus, where it produces both an acute inhibition of appetite due to food intake, and a more long-term inhibition based on the body's fat stores (Brennan and Mantzoros, 2006). Absence of leptin or genetic knockout of the leptin receptor leads to extreme obesity, as demonstrated by the ob/ob mouse. Diseases such as obesity and metabolic syndrome are associated with chronically high leptin levels (Brennan and Mantzoros, 2006); conversely, following a low-fat diet decreases circulating leptin (Dubuc et al., 1998). Both pre- and post-menopausal women have higher leptin levels than men, which may be due to endogenous estrogen levels or adipose tissue distribution (Dedeoglu et al., 2009; Rosenbaum et al., 1996; Saad et al., 1997). In premenopausal women, leptin levels correlate with plasma levels of estrogen; this correlation disappears after menopause, when it is confounded by a rise in obesity (Hong et al., 2007).

Together with leptin receptors, ERα and ERβ are expressed in the hypothalamus, although expression of ERα is greater than

ERβ (Brown et al., 2010). There is evidence that changing estrogen levels across the estrus cycle regulate leptin receptor expression at the mRNA level, likely through an ERE located on the leptin receptor gene (Bennett et al., 1999). The result of this regulation is higher sensitivity to leptin when estrogen levels are higher (Brown et al., 2010). Crosstalk between leptin receptors and ERs leads to activation of the Stat3/Erk pathway (Fusco et al., 2010; He et al., 2012). Shp2, a nonreceptor tyrosine phosphatase, has been proposed to mediate this cross-talk between leptin receptors and ERs (He et al., 2012). Analyses show that Shp2 associates with ERα, and that it is through this association that leptin and estrogen synergistically activate the Erk signaling pathway. The interaction between leptin and estrogen signaling pathways provides a mechanistic rationale for the observation that postmenopausal women may have a reduced response to leptin once estrogen levels decrease, which could lead to the increased obesity seen after menopause.

There is no consensus as to whether leptin levels increase, stay the same, or even decrease after menopause, and each of these has been reported by multiple clinical studies (reviewed by Dedeoglu et al. (2009)). This is likely due to age differences between the populations studied in each trial. One group showed that total body fat and subcutaneous fat were more predictive of leptin levels than visceral fat; as the menopausal transition is typically associated with a redistribution of adipose tissue from subcutaneous to visceral fat stores, this could account for decreased leptin after menopause (Dua et al., 1996). However, menopause is also associated with more weight gain, which could lead to an increase in leptin levels.

Studies using rat ovariectomy models showed that after OVX, rats retain the sensitivity to estrogen signaling effects on leptin, which is promising for studies of hormone therapy (Machinal et al., 1999). Clinical studies have shown that women on HT typically have both better maintenance of weight and healthier leptin levels (which could refer to an increase or decrease in leptin depending on overall metabolic status), although it is unclear which of these the principal driving force - or, again, if the driving forces are bidirectional (Dedeoglu et al., 2009; Di Carlo et al., 2004). However, other studies show that once BMI is corrected for, the association between HT and healthier leptin levels disappears (Bednarek-Tupikowska et al., 2006; Gower et al., 2000).

A typical feature of AD is decreased BMI over the course of the disease. One hypothesis is that this could be due to a disruption in energy homeostasis; thus, some recent studies have investigated whether leptin levels are associated with AD. *In vitro* and *in vivo*, leptin has a multitude of beneficial effects. A recent review summarized much of the preclinical research on leptin as it relates to AD; critically, apart from leptin's effects in the hypothalamus, there is a significant amount of research showing that leptin has neurogenic and neuroprotective actions in the hippocampus (Paz-Filho et al., 2010). *In vitro*, leptin activates the AMPK signaling pathway (Greco et al., 2011), which is critical for stimulation of neuronal energy production, either through glucose or lipid metabolism (Salminen et al., 2011). Further, there is also evidence that Aβ production and tau phosphorylation can be mediated through the AMPK pathway (Greco et al., 2009a,b, 2008; Salminen et al., 2011). Additionally, leptin decreased the amount of neurodegeneration caused by Aβ (Perez-Gonzalez et al., 2011). Similar effects were seen both in the CRND8 mouse model of AD (Greco et al., 2010), and in rabbits (Marwarha et al., 2010), where treatment with leptin decreased both amyloid burden and phosphorylated tau in the hippocampus. Leptin has also been shown to reduce neuronal β-secretase activity as well as APOE-dependent Aβ uptake (Fewlass et al., 2004). In the APP/PS1 mouse model of AD, leptin treatment increased proliferation of neuronal precursors in the dentate gyrus subgranular zone (Perez-Gonzalez et al., 2011).

In healthy elderly individuals, higher leptin levels are associated with higher gray matter volumes in the hippocampus (Narita et al., 2009) and less cognitive decline (Holden et al., 2009). Longitudinal studies have shown that both women and men with higher baseline levels of leptin have a decreased risk of incident AD (Lieb et al., 2009). Leptin levels decrease as severity of AD increases, and AD patients typically have lower leptin levels than controls (Bigalke et al., 2011; Warren et al., 2012). This is primarily due to a decrease in BMI over the course of the disease. However, it should be noted that some studies report no difference in leptin levels between AD patients and controls (Theodoropoulou et al., 2012). This may be due to differences in weight loss: one study reported that AD patients who experienced significant weight loss had lower leptin levels than those whose weight remained stable (Power et al., 2001).

5.5. Estrogen and ghrelin

Ghrelin, another of the adipokines, is the counterpart to leptin. It is the only known appetite-stimulating hormone, and it is predominantly produced by the stomach (Inui et al., 2004; Nakazato et al., 2001). Ghrelin binds to the growth hormone secretagogue receptor (GHSR) in the hypothalamus (De Vriese and Delporte, 2007), where it stimulates the release of growth hormone. There are also ghrelin receptors in the hippocampus (Carlini et al., 2004), and ghrelin has been shown to increase dendritic spine density and promote long-term potentiation (Diano et al., 2006). There is not a clear consensus as to whether women naturally have higher ghrelin levels or if levels are the same between the sexes (Makovey et al., 2007). However, both men and women show an age-related decline in plasma ghrelin levels (Rigamonti et al., 2002) and growth hormone release in response to ghrelin stimulation (Broglio et al., 2003).

Analyses of ovarian hormone regulation of ghrelin indicate that both plasma ghrelin levels and ghrelin mRNA levels in stomach cells increased after ovariectomy, and these effects were reversed with E_2 treatment. Additionally, ghrelin has been shown to colocalize with ERα in stomach (Matsubara et al., 2004). This suggests that estrogen is a negative regulator of ghrelin synthesis and thus ghrelin levels would be expected to increase following menopause. However, several studies have shown that HT has no effect on ghrelin levels in postmenopausal women (Lambrinoudaki et al., 2008; Purnell et al., 2003). One study reported increased ghrelin levels in receiving oral HT whereas transdermal HT had no effect (Kellokoski et al., 2005). Another study found that ghrelin levels increased in general over a 1.5 year period; surprisingly, ghrelin levels increased most sharply in those women who initiated and discontinued HT within the 1.5 years of the study (Soni et al., 2011). Conversely, in a study of obese women with metabolic syndrome, HT decreased ghrelin levels (Chu et al., 2006). These findings indicate that HT induces an increase or decrease in ghrelin levels based on metabolic status.

In vitro, ghrelin improves glucose/insulin homeostasis by decreasing insulin resistance, while also decreasing tau phosphorylation via activation of GSK3β (Chen et al., 2010). *In vivo*, administration of ghrelin agonists has been shown to improve cognition (Atcha et al., 2009) and neurogenesis (Moon et al., 2009). Additionally, ghrelin can protect against synaptic loss and neuronal degeneration induced by Aβ injection into the hippocampus (Moon et al., 2011).

Most studies show that plasma ghrelin levels are the same between AD patients and controls (Proto et al., 2006; Theodoropoulou et al., 2012). However, when challenged with a glucose load, male AD patients had a smaller area-under-the-curve measurement for ghrelin levels (Theodoropoulou et al., 2012). Re-

duced ghrelin mRNA levels have been observed in the temporal gyrus of patients with AD (Gahete et al., 2010).

5.6. Estrogen and adiponectin

Adiponectin is the predominant adipokine regulating overall body metabolism and development of the metabolic syndrome (Hanley et al., 2007). It is produced by adipose tissue, and regulates peripheral glucose and insulin levels (Diez and Iglesias, 2003; Dridi and Taouis, 2009). Plasma adiponectin levels are inversely correlated with glucose and insulin levels, and lower adiponectin leads to insulin resistance and dyslipidemia (Cai et al., 2012; Dridi and Taouis, 2009). Further, higher adiponectin levels are associated with lower risk of incident diabetes in prospective studies (Li et al., 2009; Zhu et al., 2010). Adiponectin also appears to play a role in inhibiting inflammatory processes (Hatzis et al., 2013). Adiponectin levels are higher in females than males (Andreasson et al., 2012; Hotta et al., 2000) and increase with age in both sexes (Andreasson et al., 2012; Obata et al., 2012). Unlike leptin and ghrelin – which exert their peripheral effects via the hypothalamus – adiponectin effects appear to be primarily peripherally mediated (Ukkola and Santaniemi, 2002).

Evidence points to ERα as a positive regulator of adiponectin levels in adipose tissue. The balance between ERα and ERβ signaling in adipose tissue changes after menopause, with ERβ becoming the dominant ER (Tomicek et al., 2011). Higher ERβ signaling leads to inhibition of peroxisome proliferator activated receptor gamma (PPARγ), which regulates secretion of adiponectin (Foryst-Ludwig et al., 2008). *In vivo* studies support this: in rats, OVX was associated with increased ERβ, decreased PPARγ, decreased plasma adiponectin levels and also decreased expression of one adiponectin receptor isoform (Tomicek et al., 2011). Further evidence of positive regulation of adiponectin through ERα comes from a study using αERKO mice; these animals had lower PPARγ levels and decreased adiponectin compared to WT mice (Ribas et al., 2010). Similarly, in humans, a particular ERα gene polymorphism that is associated with poorer prognosis after myocardial infarction is also associated with lower serum levels of adiponectin (Yoshihara et al., 2009).

Although there is a slight increase in adiponectin with age, there does not appear to be a significant difference in adiponectin levels associated specifically with menopause (Ahtiainen et al., 2012) or loss of ovarian hormones (Benetti-Pinto et al., 2010). Soni *et al* found that adiponectin levels increase slightly over 1.5 years in postmenopausal women, but this increase was driven by an increase in adiposity (Soni et al., 2011). As with leptin and ghrelin, and effect of HT on adiponectin is varied, likely because of different HT formulations in different populations. Several studies show increased adiponectin levels in women taking HT (Christodoulakos et al., 2008; Ruszkowska et al., 2013), whereas one study reported decreased adiponectin levels with HT (Im et al., 2006).

A recent study reported that individuals with MCI and AD have higher adiponectin levels both in CSF and plasma (Une et al., 2011). However, other studies have shown no difference in plasma adiponectin levels between AD patients and healthy controls (Bigalke et al., 2011; Warren et al., 2012). The Framingham Heart Study found that a higher baseline adiponectin levels was associated with increased risk of incident AD only in women (van Himbergen et al., 2012). Thus it is unclear if adiponectin itself is associated with AD development, or if it is more closely associated with metabolic disorders – such as obesity (Ukkola and Santaniemi, 2002) or metabolic syndrome (Renaldi et al., 2009) – either of which would increase an individual's risk for AD.

5.7. Estrogen and sex hormone binding globulin

Sex hormone-binding globulin (SHBG) is a glycoprotein that binds to hormones as they circulate in the bloodstream. It is produced in the liver, and its production is stimulated by estrogen and testosterone (Plymate et al., 1988). SHBG has different affinities for different hormones; it binds testosterone with a very high affinity, and its affinity is less for estrogen (Wallace et al., 2013). Traditionally it was thought that only unbound ("free") hormones were able to act on their respective receptors, and through this mechanism SHBG could influence the bioavailability of hormones. However, recent evidence indicates that there is also a G-protein-coupled receptor which binds SHBG on cell membranes (Rosner et al., 2010; Wallace et al., 2013). The SHBG receptor mechanism of action is not yet known; it may allow the bound hormone to have intracellular effects without entering the cell (Rosner et al., 1999), or it may allow the SHBG-hormone complex to enter the cell through endocytosis (Hammes et al., 2005). SHBG binding to its receptor may also prompt expression of estrogen or testosterone receptors on the cell membrane (Wallace et al., 2013). Signaling through the G-protein-coupled receptor promotes intracellular release of cAMP and activation of PKA (Rosner et al., 2010). Interestingly, SHBG bound to estrogen has agonist effects on the intracellular signaling cascade, and SHBG bound to testosterone has antagonist effects (Rosner et al., 2010).

SHBG levels are closely associated with metabolism; in particular, several *in vitro* and *in vivo* studies have shown that insulin can inhibit the synthesis of SHBG, decreasing the amount available to bind hormones and increasing hormone bioavailability (Nestler, 1993; Plymate et al., 1988). In humans, there tends to be an inverse relationship between plasma insulin level and SHBG concentration (Akin et al., 2009; Preziosi et al., 1993), which implicates severity of insulin resistance in determining SHBG levels. Insulin resistance and SHBG concentration have been examined in a number of clinical studies, and it has been consistently shown that low SHBG levels correlate with higher HOMA-IR scores (Akin et al., 2007, 2009; Davis et al., 2012b; Kalish et al., 2003; Li et al., 2010; Yasui et al., 2007). This relationship appears independent of BMI (Davis et al., 2012b), but may be mediated by abdominal obesity (Akin et al., 2009). SHBG is also associated with diabetes risk, and higher plasma levels of SHBG have been linked to lower risk of developing T2DM (Ding et al., 2006, 2009; Kalyani et al., 2009).

Women on average have higher SHBG levels than men (Bukowski et al., 2000; Soriguer et al., 2012) (http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/9285). It is unclear whether SHBG levels change with menopause after correcting for changes in insulin levels. Multiple clinical studies have measured plasma SHBG concentrations in pre- and post-menopausal women, and most (Akin et al., 2009; Key et al., 2011; Pasquali et al., 1997) but not all (Burger et al., 2000) have found no effect of menopause status on SHBG levels. The Study of Women's Health Across the Nation found that overall, there were no significant longitudinal changes in SHBG across the menopause transition, and any small decreases in SHBG levels were driven by changes in adiposity (Wildman et al., 2012). Interestingly, however, some studies have found that the inverse association between HOMA-IR and SHBG levels is only seen in postmenopausal, not premenopausal, women (Akin et al., 2007, 2009; Davis et al., 2012b). After menopause, type of hormone therapy can also affect SHBG levels; based on a number of small clinical studies, oral E_2 therapy increases plasma SHBG levels, whereas transdermal therapy has no effect (Selby et al., 1989; Taskinen et al., 1996; Vehkavaara et al., 2000) (reviewed in Goodman (2012)).

Several studies have detected higher SHBG levels in persons with AD relative to healthy controls (Hogervorst et al., 2004; Hos-

kin et al., 2004; Paoletti et al., 2004). In a recent longitudinal study, elderly men and women who were dementia-free at baseline had a greater risk of incident dementia and AD as their SHBG levels increased (Muller et al., 2010). The increased risk remained significant even after correction for age and BMI; however, it is still unclear whether this increased risk was associated with bioavailable testosterone, or whether it was perhaps associated with another dementia risk factor (such as insulin resistance or diabetes).

6. PET imaging of brain bioenergetic deficits in aging and Alzheimer's disease

Positron emission tomography (PET) scanning using fluorodeoxyglucose (FDG, a radioisotope of glucose) is a strategy to assess metabolic activity of the brain. The FDG-PET signal is particularly relevant to glucose required for synaptic activity (Landau et al., 2011). In healthy normal individuals, some studies have shown no significant differences in the cerebral metabolic rate of glucose uptake (CMRglu) between the genders (Miura et al., 1990; Tyler et al., 1988), whereas others have shown that females have higher CMRglu rates than males (Andreason et al., 1994; Yoshii et al., 1988). However, none of the studies above corrected for estrogen and progesterone levels, and it has been shown that in premenopausal women there are differences in glucose metabolism based on phase of the menstrual cycle (Reiman et al., 1996a). Thus, it is difficult to discern whether estrogen and progesterone support the same levels of CMRglu as testosterone. In normal aging, CMRglu declines with age, with the most significant declines occurring in the prefrontal cortex (Chetelat et al., 2013; Kalpouzos et al., 2009; Pardo et al., 2007). In the menopausal female brain, this age-related decline in glucose metabolism in prefrontal cortex has been detected, as well as a decline in glucose metabolism in the posterior cingulate that was specific to estrogen deprivation (Rasgon et al., 2005). In a separate study, women had a greater age-related metabolic decline than men (Murphy et al., 1996b).

A reduced rate of brain glucose metabolism is one of the most frequently documented abnormalities in AD. Alzheimer's patients show a specific pattern of abnormal glucose metabolism in regions of the brain that are most vulnerable to development of pathology, including the temporoparietal cortex, posterior cingulate, hippocampus, and precuneus (Bero et al., 2011; Jagust et al., 2007; Mosconi et al., 2009b; Vaishnavi et al., 2010; Vlassenko et al., 2010). In at-risk populations, a decline in cerebral glucose utilization appears decades prior to the onset of clinical AD (Chen et al., 2011; de Leon et al., 2001; Mosconi et al., 2009b; Reiman et al., 2004) and precedes brain atrophy (De Santi et al., 2001). Decreased glucose uptake correlates with degree of cognitive impairment as measured by the MMSE or the Alzheimer's Disease Assessment Schedule—Cognition subscale (ADAS-Cog) (Habeck et al., 2012; Minoshima et al., 1997), as well as with lower cerebrospinal fluid (CSF) Aβ42 and higher total tau and phospho-tau levels (Petrie et al., 2009).

In persons with mild cognitive impairment, glucose hypometabolism accurately predicts future clinical progression to AD (Chen et al., 2011; Chetelat et al., 2003; Herholz et al., 2011; Landau et al., 2010; Walhovd et al., 2010). The hallmark pattern of hypometabolism in AD can be detected in the aging brain long before the diagnosis of AD (Jagust et al., 2006; Mosconi et al., 2008). In fact, FDG-PET measurements of glucose metabolism are more closely related to changes in cognitive status than CSF or PET measurements of Aβ42 (Jagust et al., 2009).

Consistent with clinical findings, multiple mouse models of AD display a pattern of reduced metabolism in the posterior cingulate/retrosplenial cortex (Nicholson et al., 2010; Valla et al., 2008, 2006b). Specifically, the triple transgenic Alzheimer's disease (3xTgAD) mouse, which has a measurable decline in mitochondrial enzyme activity at 3 months and develops noticeable plaques by 6 months of age (Yao et al., 2009), has reduced metabolism that is evident as early as 2 months of age (Nicholson et al., 2010). During reproductive senescence, both the normal and 3xTgAD brain show a significant decline in glucose metabolism, which is also evident in the ovariectomized mouse (Ding et al., 2013a,b).

7. Estrogen and hormone therapy, the timing hypothesis, and risk of Alzheimer's disease

It has been proposed that the loss of estrogen after menopause could significantly contribute to cognitive decline and AD risk in women (Brinton, 2008b). Based on estrogen's myriad positive effects on mitochondrial energy production and regulation of Aβ accumulation, it seems reasonable to think that estrogen replacement after menopause would have beneficial effects on cognition in general, and might even be able to reduce the risk of AD. Epidemiological studies and clinical trials of hormone therapy and cognition have shown mixed results (Hogervorst et al., 2000; van Amelsvoort et al., 2001). The prevailing data indicate that although HT cannot alter the progression of AD (Asthana et al., 2001, 1999; Henderson et al., 2000; Mulnard et al., 2000; Wang et al., 2000), it may have the potential to lower the risk of women developing AD in the first place (Wise et al., 2001). Results from several longitudinal studies of HT use in postmenopausal women indicate that long-term HT helps to preserve memory (Jacobs et al., 1998; Maki et al., 2001; Resnick et al., 1997). Most studies also show that HT is associated with better cognitive function in nondemented older women (Duka et al., 2000; Jacobs et al., 1998; Kimura, 1995; Resnick et al., 1997; Robinson et al., 1994; Steffens et al., 1999), although one found no effect of HT on cognitive function (Barrett-Connor and Kritz-Silverstein, 1993). Multiple epidemiological studies – but not all - show that HT reduces the risk of AD, which researchers suggest may be due to delayed disease onset (Henderson et al., 1994; Kawas et al., 1997; Paganini-Hill and Henderson, 1996; Simpkins et al., 1994; Tang et al., 1996; Yaffe et al., 1998; Zandi et al., 2002).

Results from several imaging studies support the idea that postmenopausal HT can modulate brain bioenergetics, likely leading to the maintenance of cognitive function and reduced risk of AD. In the earliest study of brain metabolism in healthy postmenopausal women who were or were not receiving HT, patterns of regional cerebral blood flow (rCBF) were measured during various memory-related tasks (Resnick et al., 1998). Women taking HT showed a different pattern of rCBF than women not taking HT that was particularly evident in brain regions involved in memory systems, and the women taking HT also had superior performance on memory tasks (Resnick et al., 1998). In a follow-up study of the same women two years later, HT users showed increased rCBF over time compared to nonusers in the hippocampus, parahippocampal gyrus, and temporal lobe, regions that are critical for memory formation and are also vulnerable to decreased glucose metabolism in preclinical AD (Maki and Resnick, 2000). As before, the HT users scored higher on a battery of memory tests than nonusers (Maki and Resnick, 2000).

Glucose metabolism in cognitively intact women who were currently taking (ERT+) and had never taken (ERT-) estrogen replacement therapy, as well as women with clinically diagnosed AD, has also been studied using FDG-PET (Eberling et al., 2000). The ERT+ cohort had the highest rates of glucose metabolism, and their metabolic rates were significantly higher than those seen in the women with AD. Women in the ERT- cohort had glucose metabolism rates that were intermediate to the two other groups, but their rates were not significantly different from the women

with AD (Eberling et al., 2000). This provides evidence that estrogen depletion can affect glucose metabolism. Similarly, a longitudinal study compared glucose metabolism between cognitively healthy women who did and did not take hormone therapy. At baseline, the two groups of women showed no differences in metabolism; after two years, the women not on hormone therapy had a significant decrease in glucose metabolism in the posterior cingulate cortex – an area of the brain which shows metabolic decline in the earliest stages of AD – whereas the women receiving estrogen therapy did not have a significant metabolic change in this brain region (Rasgon et al., 2005). This preservation of brain metabolism was later shown to be greatest in women taking 17β-estradiol-based hormone therapy formulations (Silverman et al., 2011). Although these studies are observational, they provide evidence that peri- or postmenopausal HT has a positive effect on brain bioenergetic function in women.

A challenge for the field was that results from the Women's Health Initiative Memory Study (WHIMS) opposed the idea that estrogen was protective against development of AD. In the WHIMS study, both women in the estrogen-alone cohort (Shumaker et al., 2004) and women in the estrogen + progesterone cohort (Shumaker et al., 2003) showed an increased risk of developing AD. However, women in the WHIMS trial were significantly older than women in many of the prior epidemiological studies: on average, they were 65 years old, which is at least a decade past menopause. Additionally, the average BMI of women enrolled in the Women's Health Initiative study (the population from which the WHIMS women were drawn) was in the overweight range, which likely would have put these women at a higher risk for metabolic diseases such as diabetes, thus increasing their risk for AD (Stefanick et al., 2003). Further – as discussed previously – the unhealthy metabolic status of these women could have potentially attenuated any positive response to hormone therapy.

Thus, a "critical window" theory of hormone replacement has been suggested, based on the concept that estrogen has beneficial effects if taken before or at the time of menopause when neurological health is still intact, but detrimental effects if initiated years after menopause when neurological health may have already begun to decline (Brinton, 2004, 2005). Model systems that have been used to investigate the role of hormone replacement after menopause fall into two distinct classes: preventative interventions in healthy organisms, and "restoration" interventions in organisms with compromised neurological function (Brinton, 2005, 2008a,b). In our laboratory, all systems that have led to the elucidation of neuroprotective effects of estrogen and underlying mechanisms of action have typically used a prevention experimental paradigm (Brinton, 2005, 2008a,b; Yao et al., 2012). Data from other researchers also supports this critical window hypothesis: estrogen replacement in rats shortly after ovariectomy is associated with in improvements in learning, whereas estrogen replacement after a long period of estrogen deprivation is disadvantageous (Daniel et al., 2006; Gibbs, 2000). Further, this prevention paradigm was investigated in women with surgical or pharmacological-induced menopause, where the beneficial effects of HT shortly after menopause paralleled the effects seen in animal model prevention studies (Phillips and Sherwin, 1992; Sherwin, 1988, 2012). An increasing body of clinical literature also supports the concept of a critical window of estrogen benefit, which aligns with the healthy cell bias of estrogen action (Bagger et al., 2005; Berent-Spillson et al., 2010; Brinton, 2008b; Henderson et al., 2005; MacLennan et al., 2006; Maki, 2013; Maki et al., 2011; Shao et al., 2012; Whitmer et al., 2011; Zandi et al., 2002).

8. Biomarkers: systems biology vs. individual markers

As reviewed above, the process of aging in the female involves a shift in bioenergetic systems. Within the brain, this is evidenced by changes in substrate supply, substrate metabolism, and mitochondrial respiration that, when combined, lead to a change from a highly efficient, glucose-driven phenotype to a less efficient, ketone-dependent phenotype (Yao et al., 2011). Peripherally, changes in glucose/insulin homeostasis and adipokine regulation of energy intake and expenditure are coincident with metabolic changes occurring in the brain. Therefore, development of peripheral biomarker profiles, rather than individual markers of components within the system, can serve as a reporter of brain metabolism.

The criteria for a biomarker of AD were proposed in 1998 by the Working Group on Molecular and Biochemical Markers of Alzheimer's Disease, and have since become standards for the field. The Working Group specified: "the ideal biomarker for AD should detect a fundamental feature of neuropathology and be validated in neuropathologically-confirmed cases; it should have a diagnostic sensitivity >80% for detecting AD and a specificity of >80% for distinguishing other dementias; it should be reliable, reproducible, non-invasive, simple to perform, and inexpensive" (Authors, 1998).

Identification of biomarkers is critical to reliably identify populations at risk for AD, and for development of interventions to prevent, delay, and treat AD. Conceptualization of Alzheimer's disease is shifting from a disease initiated by a single pathological entity to a failure of multiple interacting systems (Yao et al., 2011). A systems-level perspective predicts that failures at different points within the system can differentially affect future risk of developing AD. This conceptualization predicts that biomarker profiles which define an individual's risk may shift over time and during the prodromal phase. A further prediction is that multiple therapeutic interventions that target risk phenotypes will be necessary.

Both basic science research and clinical observations suggest that menopausal loss of estrogen plays a significant role in brain aging, and can increase Alzheimer's disease risk in women (Brinton, 2008b; Paganini-Hill and Henderson, 1994). Evidence indicates that estrogen is a systems-level regulator of brain and whole-body bioenergetics, with a decline in metabolism occurring coincidentally with loss of estrogen at menopause. Of the 5.2 million Americans diagnosed with late-onset Alzheimer's disease, 3.4 million are women and 1.8 million are men (Authors, 2013). Most epidemiological studies indicate higher prevalence and greater lifetime risk of Alzheimer's disease in women (Authors, 2013; Gao et al., 1998; Seshadri et al., 2006). While prevalence of AD in women is well documented, the incidence rate of AD in women vs. men is controversial, with some studies showing higher incidence in women (Fratiglioni et al., 1997; Launer et al., 1999; Ott et al., 1998) and some showing equal incidence between the sexes (Edland et al., 2002; Fillenbaum et al., 1998; Hebert et al., 2001). Upon reviewing the effects of hormone therapy on both brain and whole-body metabolism, it is apparent that while some women may benefit from postmenopausal HT, others may experience detrimental effects. It is also clear that metabolic status can be a key factor in evaluating the risk/benefit profile of hormone therapy.

9. Conclusions

As discussed throughout this review, the decrease in estrogen that women experience during menopause leads to a wide range of changes throughout the metabolic system of the brain and body. Moreover, the tight integration of these systems predicts that alterations within one component of the system will obligate other

components to adapt. These adaptations under certain circumstances can compensate for the loss of estrogen regulation. However, such adaptations are highly individualistic. Some women will compensate very well for the rest of their life, whereas women on the other end of the adaptive spectrum will be unable to compensate. Some women will fall in between: they will be able to compensate well, but for a relatively short period of time. We hypothesize that it is women in the latter two categories of compensatory capacity who are at risk for developing late-onset Alzheimer's disease.

Critical to identifying women at risk for Alzheimer's is the development of peripheral biomarkers that serve as reporters of the bioenergetic system of the brain. Such a biomarker profile could both identify women at risk and serve as an indicator of therapeutic efficacy. Further, the efficacy of hormone therapy formulations to sustain bioenergetic system function could be assessed using this same biomarker profile.

Acknowledgments

The authors would like to acknowledge Dr. Wendy Mack and Dr. Enrique Cadenas for helpful discussions throughout the process of developing this manuscript which have enriched our understanding of the complexities of human populations and the metabolic system. Funding for development of this review and our research was supported by R01AG032236 (to R.D.B.), P01AG026572 (to R.D.B. and W.M.), R01AG033288 (to R.D.B.), and F31AG044997 (to J.R.R.).

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