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Opinion

Sex differences in Alzheimer's disease: metabolic reprogramming and therapeutic intervention

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Studies on the sporadic form of Alzheimer's disease (AD) have revealed three classes of risk factor: age, genetics, and sex. These risk factors point to a metabolic dysregulation as the origin of AD. Adaptive alterations in cerebral metabolism are the rationale for the Metabolic Reprogramming (MR) Theory of the origin of AD. The theory contends that the progression toward AD involves three adaptive events: a hypermetabolic phase, a prolonged prodromal phase, and a metabolic collapse. This article exploits the MR Theory to elucidate the effect of hormonal changes on the origin and progression of AD in women. The theory invokes bioenergetic signatures of the menopausal transition to propose sex-specific diagnostic program and therapeutic strategies.

Highlights

The Amyloid Cascade Hypothesis has dominated the studies on the etiology of AD over the past 30 years Therapeutic interventions that this model involves have consistently failed until now.

Age and gender are the two most salient risk factors for the origin and progression of sporadic AD. The effect of these two factors on the incidence of AD derives from age-related mitochondrial alterations and the hormonal changes affecting postmenopausal women.

The MR Theory is a bioenergetic model of metabolic regulation in neurons and astrocytes during aging. It postulates that AD is the result of age-related bioenergetic dysregulation. The theory furnishes an understanding of certain phenomena that appear intractable in the conceptual framework of the Amyloid Cascade Hypothesis: the long prodromal phase of AD and the rapid transition to the pathological state.

A bioenergetic origin for Alzheimer's disease

The sporadic form of AD is a neurodegenerative disorder with a multifactorial pathogenesis. Epidemiological and clinical studies have documented two classes of molecular signature that are identified with the disease: (i) bioenergetic: the critical features of this marker are metabolic defects and bioenergetic dysfunction in mitochondria, the energy-producing organelles. These abnormalities inhibit neuronal energy production and induce neuronal loss; and (ii) biochemical: the specific features of this class of signatures are misfolded proteins. These include the amyloid-β (Aβ) deposits that are the result of defective aggregation of the product of amyloid precursor protein (APP) processing, and the various intra- and extracellular neurofibrillary tangles characterized by the abnormally hyperphosphorylated tau protein.

Epidemiological studies show that the biochemical signatures often contradict the clinical observations (reviewed in [1]). Individuals with a high amyloid load are often cognitively intact and display no clinical manifestations of dementia [2]. Consistently, a meta-analysis of antiamyloid drug clinical trials (pooled results from 14 randomized controlled trials) revealed that removal of brain amyloid plaques does not improve the cognitive functions of patients with AD [3]. By sharp contrast, bioenergetic markers are highly correlated with the origin and progression of the disease (Figure 1) [4]. The support for a bioenergetics origin is further indicated by the correlation between reproductive history, hormonal changes, and the risk of AD in women [5].

These observations point to a disease origin with a critical metabolic component. The MR Theory [6,7,99], an analytic model of AD, derives from the study of the three main risk factors associated with the disease. These factors fall into three categories: (i) age: the disease has an average age of onset ~70 years. Moreover, the incidence of the disease increases exponentially with higher age; (ii) genetics: the incidence of the apolipoprotein ε4 (APOE4) allele. AD risk is increased threefold in

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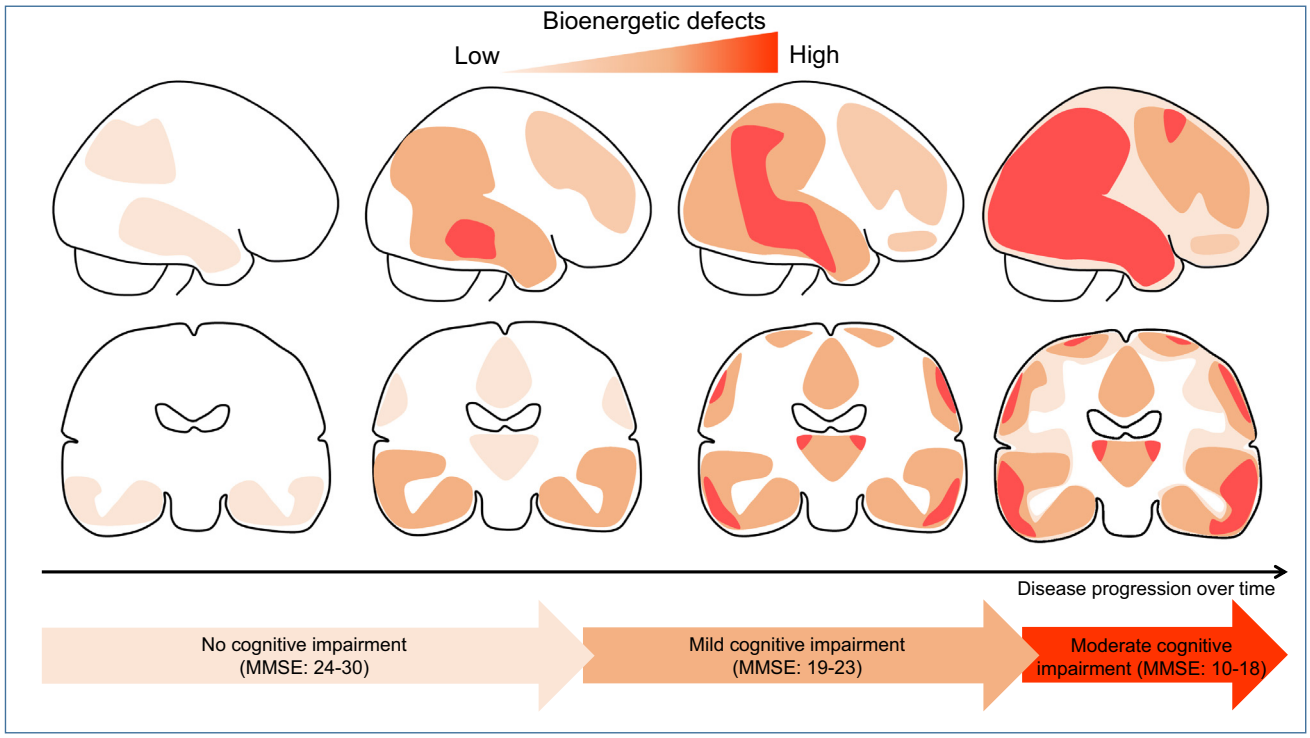

Figure 1. Simplified maps illustrating the spread of bioenergetic abnormalities in the brain during Alzheimer's disease (AD) progression. A decrease in glucose uptake appears to start in the posterior temporal and parietal cortices, as well as in the hippocampal and entorhinal regions. Bioenergetic defects then spread to the dorsolateral prefrontal and premotor cortices, as well as to deeper brain regions, including the thalamus. Interestingly, brain bioenergetics defects correlate with cognitive decline [Mini-Mental State Examination (MMSE) score] [32,33]. The upper panel shows a lateral view of the brain (right side) and the lower panel shows a coronal view.

APOE ε3/ε4 carriers, and 15-fold in APOE ε4/ε4 carriers [8]; (iii) sex: the incidence of women among AD patients is two-thirds. The main risk factor which has been identified is the decline in sex-steroid hormones in post-menopausal women [9]. These three risk factors implicate metabolic dysregulation and bioenergetic deficits as critical elements in the etiology of the disease [9–11].

In this article, we discuss the theoretical basis and empirical support for the MR Theory. We then exploit the theory to address two fundamental issues regarding the origin and progression of AD in women: (i) the formulation of AD diagnostic criteria based on metabolic changes in neurons due to the endocrine transition occurring at the menopause; and (ii) the development of therapeutic strategies to prevent the disease or to reduce its severity.

Metabolic reprogramming theory on the origin of Alzheimer's disease

The MR Theory is a bioenergetics model of metabolic regulation in neurons and astrocytes during the aging process (detailed explanation of the model reviewed in [6,7]). The theory is based on two fundamental properties of biological processes: energy and age. Energy is the prime determinant of neuronal viability. Defects in energy metabolism may lead to neuronal degeneration. Age is the decisive arbiter of the efficiency of energy production. Aging is associated with a decline in the activity of enzymes involved in metabolic regulation [10].

The MR Theory is based on the effect of the process of aging on the interaction between two cell types: neurons, whose metabolism is driven by oxidative phosphorylation (OxPhos), and astrocytes, whose metabolic activity is determined primarily by glycolysis. Both cell types use glucose as an energy source. In astrocytes, a significant portion of the glucose is metabolized aerobically to lactate, which is released into the extracellular milieu. In neurons, glucose-derived and lactate-derived pyruvate are metabolized aerobically.

The model proposes that, when some of the mitochondria in neurons become dysregulated during aging, the associated increased demand for energy is achieved by the action of two mechanisms: (i) the inverse Warburg effect (Box 1): the upregulation of OxPhos activity in some mitochondria of cortical neuronal cells. This mode of metabolic alteration is a compensatory action to maintain adequate production of energy and thereby mitigate the deficit induced by the age-related mitochondrial dysregulation; and (ii) the Warburg effect: the upregulation of glycolysis in the astrocytes, which are the nourishing cells in the brain. This process increases the activity of the astrocytic cells and, thus, enhances the production of lactate, which ensures an adequate energy source for the neurons.

The outcome of this metabolic reprogramming in neurons and astrocytes is the production of two types of neuronal population: Type 1: cells, primarily cortical neurons, with high OxPhos activity. Their mitochondrial population will be highly heterogeneous, with a few being hypermetabolic, and the large majority intact; and Type 2: cells with normal OxPhos activity. Their mitochondria will be relatively intact.

The competition between these two types of neuron for the lactate generated by the astrocytes will result in the development of three distinct phases of metabolic activity in the neuronal population (Figure 2, Key figure): (i) a hypermetabolic phase, localized in the cortical regions; (ii) a metabolic homeostasis, quasi-equilibrium defined by the presence of neurons with upregulated OxPhos activity (Type 1) and neurons with standard OxPhos activity (Type 2); and (iii) a metabolic collapse, the rapid spread of metabolic abnormalities due to a change in the neuronal environment and the concomitant selective advantage of hypermetabolic neurons.

Box 1. Inverse Warburg effect and Alzheimer's disease

Theoretical basis

OxPhos and glycolysis are the two modes of energy production in cells. The first is an electrical process the rate of which depends on the conductance of the mitochondrial membrane. The second is a chemical process the rate of which depends on the activity of the glycolytic enzymes. OxPhos generates up to 36 molecules of ATP upon complete oxidation of molecules of glucose, whereas glycolysis generates only two ATP molecules per molecule of glucose. The impairment of OxPhos due to the process of aging, for example, has a critical effect on the cellular metabolism. In non-neuronal cells, this effect elicits a compensatory shift to glycolysis. This shift from an electrical mode of energy production to a chemical mode is called the Warburg effect, for which empirical support is now well documented [69]. The Warburg effect is also observed in stressed astrocytes that provide the energy source for neurons [70]. In contrast to cancer cells, neurons rely almost exclusively on OxPhos to generate the energy needed for cellular processes. Neurons, similar to differentiated postmitotic cells, are subject to continuous stress. These insults may be the result of mutations in the genes that regulate mitochondrial activity [10]. We have proposed that, during aging, several mitochondria in certain neurons will become abnormally hypermetabolic, while a certain number will remain intact [7]. This is described by an increase in the metabolic activity of the neurons with an up-regulation in OxPhos: the inverse Warburg effect (Figure I).

Empirical support

Evidence for the inverse Warburg effect has been documented in both patients with AD and AD animal models. Indeed, several independent studies highlighted a correlation between increased OxPhos and increased oxidative damages (see also Table 1 in the main text). Hypermetabolism detected in very early AD stages [23–26,71] is likely linked to this increased OxPhos and may be a compensatory mechanism to sustain the higher energy needs of affected neurons.

Biomarker

The inverse Warburg effect (hypermetabolism in pre-AD brains) may be used as a marker for the early diagnosis of AD. Indeed, the three phases (hypermetabolism, stable metabolic phase, and hypometabolism) represent bioenergetic adaptations to age-related metabolic deregulation. The magnitude of changes in the hypermetabolic phase provides a measure of individual vulnerability to the disease. Hence, the inverse Warburg effect constitutes a bioenergetic marker for the later development of AD.

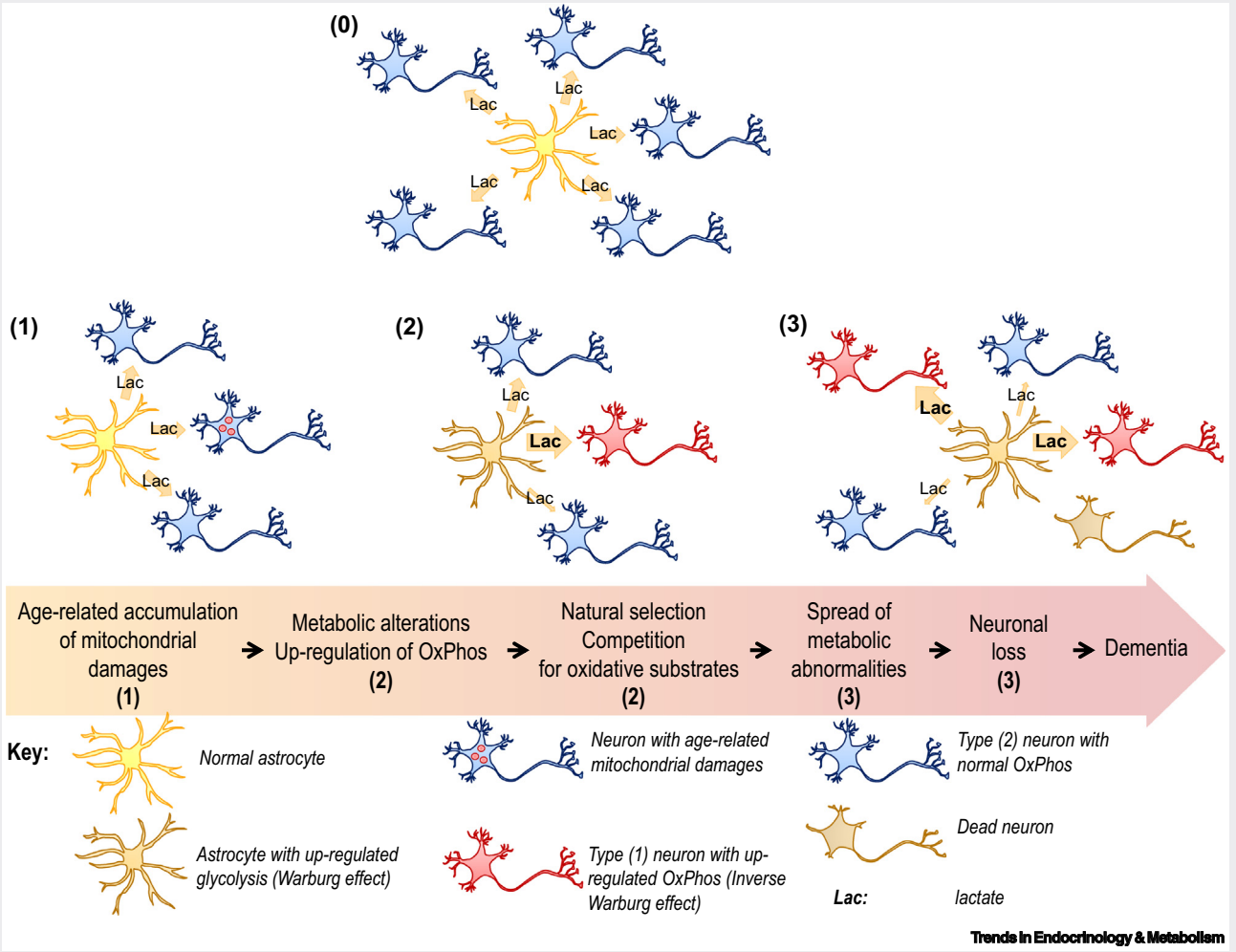

Figure I. Metabolic Reprogramming Theory and the inverse Warburg effect. (0) In normal conditions, astrocytes deliver energetic substrates to neurons (e.g., lactate). Astrocytes mainly use glycolysis to transform glucose into energy, whereas neurons mainly use oxidative phosphorylation (OxPhos) taking place into mitochondria. (1) During aging, mitochondrial dysfunctions may occur. (2) Age-related mitochondrial dysfunctions may lead to an increase in energy demand and upregulation of OxPhos in some neurons (inverse Warburg effect) and glycolysis in astrocytes (Warburg effect) as a compensatory mechanism. Neurons with normal OxPhos activity (Type 2) and neurons with upregulated OxPhos activity (Type 1) compete for energy substrates generated by astrocytes. (3) With time, Type 2 neurons do not receive enough substrate to support their needs and die (natural selection). Hypermetabolic neurons create a neuronal microenvironment, which contributes to the spread of the disease. Microvascular abnormalities (e.g., ministrokes), or additional stressors (e.g., oxidative stress) may contribute to the changes in the neuronal microenvironment. The timeline recapitulates the different steps leading to neuronal loss and dementia.

Evidence of an inverse Warburg effect and hypermetabolism in AD animal models and patients with AD is summarized in Table 1. Indeed, an upregulation of genes involved in OxPhos, including subunits of the mitochondrial complexes I, III, IV, and V, was observed in the brain of AD transgenic mice (Tg2579 and PS1-A246E mutant mice) before the appearance of Aβ pathology and before AD-related cognitive deficits were observed [12,13]. Mitochondrial abnormalities were associated with an increase in 8-hydroxyguanosine (8-OHG) level, a marker of oxidative damage [12,13]. Strikingly, an increase in brain glucose uptake was also detected in different AD mouse models (Tg2579, APP/PS1, 5xTgAD, 3xTgAD) at early stages of the pathology [14–18].

Key figure

Metabolic Reprogramming Theory and neuroendocrine transition state in females: diagnostic programs and therapeutic interventions

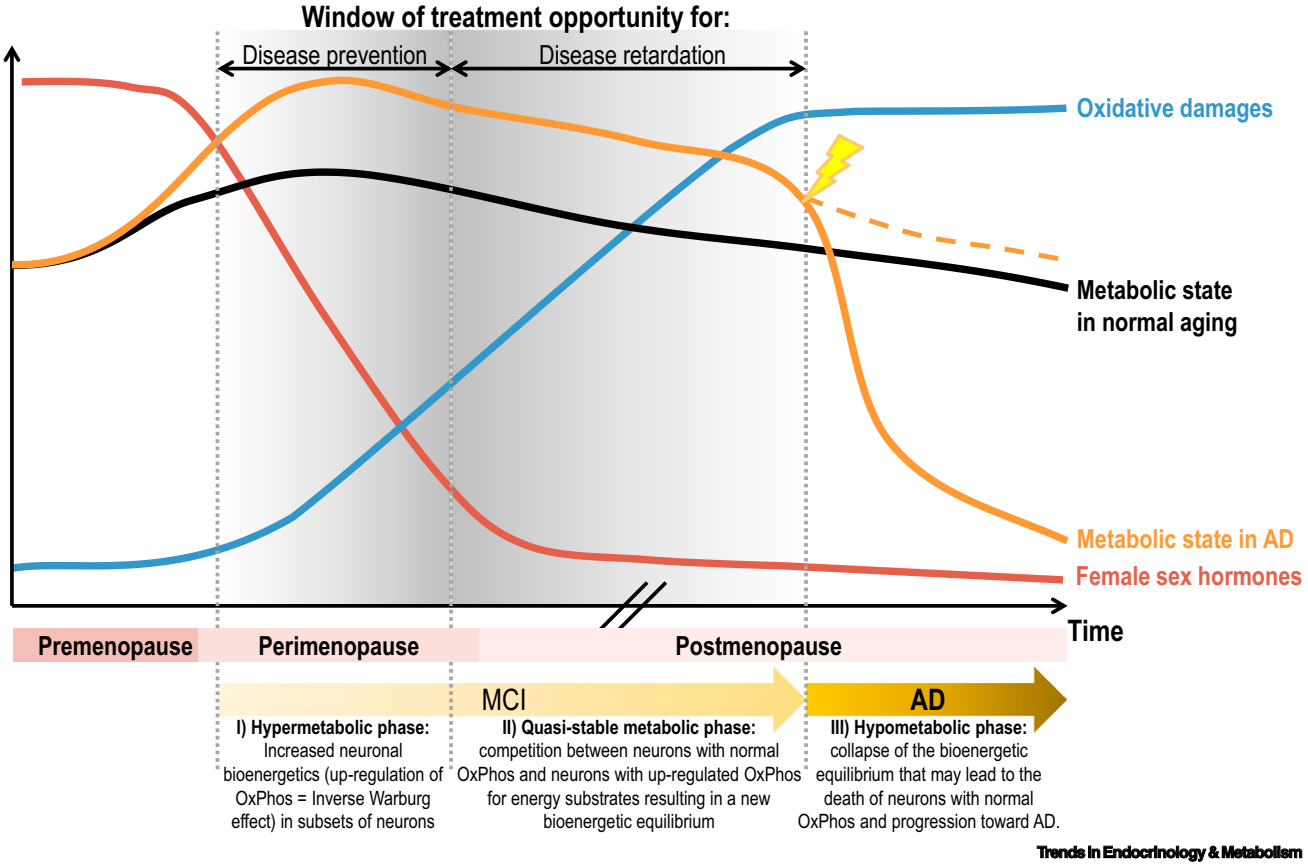

Figure 2. Three stages of metabolic states may be delineated (orange line): (i) a hypermetabolic phase at the perimenopause with upregulation of oxidative phosphorylation (OxPhos; inverse Warburg effect) in subsets of neurons to maintain adequate production of energy and to mitigate the deficit induced by the mitochondrial dysfunction caused by the loss of regulatory sex hormones; (ii) a quasi-stable metabolic phase (new equilibrium) at the 'early' postmenopause. This stage would correspond to AD prodromal phase or mild cognitive impairments (MCI); and (iii) a hypometabolic phase at the 'late' postmenopause. The lightning indicates a change in the neuronal environment (e.g., caused by a mini-stroke, mini-infarct, or high levels of oxidative damage) that disrupts the equilibrium between normal neurons and neurons with high OxPhos, leading to neuronal death. By comparison, the metabolic state in normal aging is indicated by a black line. Given that neurons with upregulated OxPhos generate more reactive oxygen species, oxidative damage progressively increases (blue line). In females, the loss of sex hormones at the menopause (pink line) is also paralleled by increased oxidative stress and disturbed brain metabolic function. A possible window of treatment opportunity is indicated. Therapeutic intervention within this time period may prevent the metabolic collapse leading to cell death. Diagnostic programs and therapeutic interventions at different menopausal stages are described. Abbreviations: DMI, deuterium metabolic imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; HRT, hormone replacement therapy.

Similar data were obtained from brains from patients with AD. Namely, an increased expression of mitochondrial complex IV subunits (COX I and COX IV), as well as an increased level of mitochondrial DNA, were detected in the hippocampus and cortex of patients with sporadic AD [19–22]. As observed in animal models of AD, neurons with upregulated OxPhos genes also presented higher oxidative damages (increased level of 8-OHG), suggesting that mitochondrial dysfunction leads to oxidative stress in AD brains [20,22]. Interestingly, brain hypermetabolism was detected in several studies at very early stages in patients with mild cognitive impairment (MCI) [23–26].

Table 1. Evidence for an inverse Warburg effect and hypermetabolism in AD mouse models and patients with AD[a]

Animal model/human	Method	Organ/tissue analyzed	Main results	Refs
Animal data				
Tg2576	cDNA microarray techniques, northern blot, *in situ* hybridization	Hippocampus (granule cells, pyramidal neurons), cerebral cortex	Upregulation of genes involved in mitochondrial energy metabolism and apoptosis in 2-, 5-, and 18-month-old Tg2576 animal compared with WT	[12]
	Brain glucose metabolism assessment using FDG-PET	Hippocampus, perirhinal cortex, entorhinal cortex, striatum, thalamus, cerebral cortex	Increase of glucose uptake in 7-month-old Tg2576 animals compared with WT	[14]
PS1-A246E mutant mice	Measure of COX activity in brain	Cortical area, striatum, forebrain cholinergic areas, limbic regions, thalamus, brainstem	Increase of COX activity in 12-month-old Tg animals compared with WT	[13]
APP/PS1 mice	Brain glucose metabolism assessment using FDG-PET	Cortex, hippocampus, striatum	Increase of glucose uptake in 6- and 12-month-old APP/PS1 animals compared with WT	[16]
	Assessment of 2DG uptake in brain (voxel-wise approach using MRI-based digital atlas)	Amygdala, anterior commissure, corpus callosum, cortex, hippocampus, olfactive bulb, striatum	Higher glucose uptake in APP/PS1 mice than in PS1 mice	[15]
3xTgAD	Assessment of metabolic rate (O_2 consumption, CO_2 production, respiratory quotient) using calorimetry over 4 days	n.i. (global metabolic rate)	Increase of metabolic rate and food intake in 12-month-old 3xTgAD mice despite weight loss compared with WT	[90]
	Assessment of neuronal and astrocytic metabolism by intravenous infusion of [1-^{13}C] glucose + [1,2-^{13}C] acetate followed by ^{13}C NMR	Whole-brain analysis, neurons, astrocytes	Hypermetabolic state detected in both neurons and astrocytes of 7-month-old 3×TgAD mice compared with WT (increase in absolute levels of different ^{13}C metabolites)	[18]
5xTgAD	Brain glucose metabolism assessment using FDG-PET	Whole-brain analysis	Increase in glucose uptake in 10-month-old 5xTgAD animals compared with WT	[17]
Human data				
Subjects with Down syndrome (DS) [*N* = 13, 35.4 years (range:0–65 years)] Patients with sporadic AD (*N* = 19, 76.6 years (range: 61.6–89.8 years) Old patients without dementia (*N* = 6, 74.3 years (range: 61.6–81.8 years)	Postmortem brain immunohistochemistry for COX I and IV expression	Hippocampus	Increased expression of COX I and IV in patients with DS or AD in nontangle-bearing neurons	[19]
Patients with early AD (*N* = 6, 67–96 years) Diagnosed AD (*N* = 6, 69–82 years) Normal control subjects (*N* = 6, 68–90 years)	Postmortem brain analysis (RT-qPCR and immunohistochemistry) of mitochondrial complex expression	Frontal cortex	Downregulation of mitochondrial genes in complex I in both early and definite AD brains, but upregulation of complexes IV and V compared with control brains	[22]
Patients with AD (*N* = 27, 57–93 years) Normal control subjects (*N* = 12, 54–85 years)	*In situ* hybridization for analysis of mitochondrial DNA (mtDNA) Immunocytochemistry for COX I expression	Hippocampus	Increased levels of mtDNA and COX I, but decreased number of total mitochondria per neuron in AD brains compared with age-matched control brains	[20,21]
Patients with AD (*N* = 10, 79.9 ± 9 years) Normal control subjects (*N* = 9, 61.8 ± 15 years)	Postmortem brain analysis of mitochondrial complex expression	Whole hippocampus and hippocampal pyramidal neurons	Upregulation of OxPhos genes (complexes I–IV) in whole hippocampus of patients with AD compared with controls, but downregulation of these genes in pyramidal neurons	[91]

Table 1. (continued)

Animal model/human	Method	Organ/tissue analyzed	Main results	Refs
hiPSCs derived from patients with AD (*N* = 5) Control subjects-derived IPSCs (n = 2)	Gene expression analysis (OxPhos genes) in hiPSC-derived neurons	hiPSC-derived neurons	Upregulation of OxPhos genes (complexes I, III, IV) in hiPSCs derived from patients with AD compared with controls	[28]
Middle-aged patients without dementia but with DS (*N* = 17, 41.4 ± 5.6 years) Patients with moderate AD (*N* = 10, 76.0 ± 6.7 years) Age-matched control subjects (*N* = 24)	Glucose metabolic rate (GMR) determination using FDG-PET	Multiple areas of inferior temporal cortex (including area of entorhinal cortex)	GMR higher in DS group compared with matched controls; GMR lower in patients with AD compared with matched controls	[71]
Patients with MCI (14 amyloid-positive and amyloid-negative, 73.1 ± 6.5 years) AD patients (14 amyloid-positive, 72.1 ± 9.7) Normal control subjects (14 amyloid-positive, 70.8 ± 7.6 years; 24 amyloid-negative, 72.6 ± 5.3 years)	FDG-PET (brain glucose metabolism); PiB PET (presence of amyloid)	Anterior cingulate, precuneus/parietal cortex	Negative correlations between PiB retention and metabolism in patients with AD; frequent significant positive correlations between metabolism and PiB retention in patients with MCI	[25]
Patients with stable MCI (MCI-S; stable for 24 months, *N* = 148, 75.26 ± 7.10 years)Patients with progressive MCI (MCI-P; progressed to AD, *N* = 39, 75.83 ± 7.22 years) Patients with AD (*N* = 60, 75.25 ± 7.26 years) Normal control subjects (*N* = 26, 75.69 ± 5.68 years)	FDG-PET homeostasis model assessment of insulin resistance (HOMA-IR)	Lateral parietal and posteromedial cortices, medial temporal lobe, hippocampus, ventral prefrontal cortices, postcentral gyrus, global cerebrum control regions	Lower FDG metabolism in a stepwise manner from normal subjects to MCI to AD; for MCI-P, higher HOMA-IR predicted higher FDG (hypermetabolism). For AD, higher HOMA-IR predicted lower FDG and hypometabolism	[26]
Patients with MCI (*N* = 10, 66 ± 9.9 years)Patients with AD (*N* = 9, 65.6 ± 6.6 years) Control subjects for FDG (*N* = 8, 64.9 ± 5.9 years) Control subjects for PiB (*N* = 14, 64.4 ± 5.9 years)	FDG-PET (brain glucose metabolism); PiB PET (presence of amyloid)	Anterior cingulate, posterior cingulate, frontal, temporal, parietal and occipital cortex, hippocampus, parahippocampal gyrus, amygdala, precuneus, thalamus, striatum, precentral and postcentral gyrus	Cortical hypermetabolism observed in four amyloid-negative patients with MCI (did not convert to AD) and one amyloid-positive patient; hypometabolism observed in five patients with MCI with high amyloid load (four converted to AD)	[23]
Patients with MCI converted to AD (MCI-C; *N* = 87, 75 ± 7 years) or patients with MCI non-converted to AD (MCI-nc; *N* = 185, 74 ± 8 years)	FDG-PET; princple components analysis (PCA); AD conversion-related pattern (ADCRP)	Temporoparietal, frontal, posterior cingulate, and precuneus cortices; sensorimotor and occipital cortices, cerebellum, left putamen	PCA revealed ADCRP that involved regions with hypometabolism and hypermetabolism	[24]

[a]Abbreviations: 2DG, 2-deoxyglucose; COX, cytochrome c oxidase (complex IV); FDG-PET, [18F] fluorodeoxyglucose positron emission tomography; hiPSC, human induced pluripotent stem cells; NMR, nuclear magnetic resonance; MRI, magnetic resonance imaging; n.i., not investigated; WT, wild-type.

At the cellular level, it was shown that fibroblasts derived from patients with late-onset AD exhibited an impaired mitochondrial metabolism together with a shift in energy production to glycolysis [27]. Given that fibroblasts are proliferating cells, the increased glycolysis (Warburg effect) is probably a compensatory mechanism against mitochondrial impairments. Strikingly, human induced pluripotent stem cell-derived neurons (hiPSCs) from patients with sporadic AD showed an increased level of OxPhos chain complexes, paralleled with an increased reactive oxygen species (ROS) level and DNA damage [28]. These data might reflect an inverse Warburg effect in these nonproliferating human neuronal cells, and suggest a constitutional metabolic changes in neurons from subjects prone to develop AD pathology.

The rationale for the condition of the two phases (metabolic homeostasis and metabolic collapse) is the Entropic Selection Principle [29,100]. This asserts that the outcome of competition for substrates between neuronal populations is contingent on the neuronal environment and the metabolic rate of the population: (i) when the neuronal substrates are scarce, neurons with higher metabolic rate have a selective advantage. They will outcompete neurons with lower metabolic rate and, thus, increase in frequency; and (ii) when the neuronal environment is abundant, neurons with a lower metabolic rate will outcompete neurons with higher metabolic rate and, thus, increase in frequency.

The MR Theory recognizes that neurons differ in their demand for energy compared with nonexcitable, mitotic cells. Consequently, they will differ in terms of their vulnerability to mitochondrial dysregulation. The neurons providing the projection from entorhinal cortex to the dentate gyrus appear to be the most vulnerable cell type in AD. The pyramidal neurons within the Ca1 part of the hippocampus, as well as those connecting the association regions of temporal, prefrontal, and parietal areas, are also highly sensitive to insults, such as energy deprivation [30,31]. The vulnerability of these hippocampal and cortical circuits may explain the disease progression (cognitive decline) that appears to correlate with the spreading of bioenergetics abnormalities in the brain, namely glucose hypometabolism (Figure 1) [32–34]. Of note, because healthy aging is also marked by a slight decrease in brain glucose metabolism, bioenergetics alterations related to AD are more salient in young patients (50–60 years of age) and correlate with the Mini-Mental State Examination (MMSE) score, a widely used test evaluating cognitive impairments [32,33].

The MR Theory furnishes an understanding of certain phenomena that appear intractable in the conceptual framework of neuron-centric models, such as the Amyloid Cascade Hypothesis.

These phenomena and the argument in terms of MR Theory include: (i) the long prodromal phase of AD: this condition derives from the stable coexistence of Type 1 neurons (defined by upregulated OxPhos activity) and Type (2) neurons (with normal OxPhos activity). This stability, a consequence of the neuronal environment, is provided by the enhanced lactate production of the astrocytes. This prodromal phase may be considered as a stage occurring before a clinical diagnosis of AD is made. It also refers to MCI, which is a stage that possibly starts at the onset of bioenergetic impairments (Figure 2); and (ii) hypometabolism and the rapid transition to the pathological state: this situation may be triggered by cerebral perfusion, a result of cerebrovascular lesions, such as a mini-stroke or micro-infarcts. These vascular disorders induce changes in the neuronal environment and confer a selective advantage to Type 1 neurons by decreasing the viability of Type 2 neurons.

Bioenergetic impairments and AD-related protein hallmarks in the context of the MR Theory

Substantial evidence has shown bioenergetic impairments in *in vitro* and *in vivo* AD models (reviewed in [35,36]). Bioenergetic dysfunctions were identified as an early event of the diseases, occurring even before the appearance of both AD protein hallmarks, Aβ plaques and neurofibrillary tangles (tau pathology), as well as before the cognitive deficits [36,37]. As stated earlier, brain bioenergetic changes are correlative with the disease progression, namely glucose hypometabolism and cognitive decline [30,32,33]. Therefore, brain bioenergetic metabolism appears to be a better biomarker for AD diagnosis and progression compared with Aβ or tau pathology.

Empirical evidence of the inverse Warburg effect in AD animal models and patients with AD showed that neurons with upregulated OxPhos presented an increase in oxidative insults [12,13,20,22,28]. Indeed, mitochondria can be compared to a double-edged sword that, on

the one hand, produces necessary cellular energy and, on the other hand, induces the formation of harmful ROS. Strikingly, ROS themselves trigger Aβ generation by enhancing the amyloidogenic pathway [38–43]. Similarly, increased levels of tau and tau abnormal phosphorylation were observed in mice lacking the detoxifying enzyme superoxide dismutase 2 (SOD2) [44]. Together, these data suggest that the increase in mitochondrial ROS levels leads to enhanced Aβ formation and tau pathology. Besides, substantial evidence has shown that Aβ and abnormal tau can, in turn, affect mitochondrial function, triggering a vicious cycle of oxidative stress [10,35,36,45].

In the context of the MR Theory, we can hypothesize that the upregulation of OxPhos activity (inverse Warburg effect), to compensate age-related mitochondrial dysfunction, is paralleled by an increase in ROS production by mitochondria. These ROS may lead to proteinopathies (Aβ and Tau pathology), which furthermore exacerbate bioenergetic impairments. Therefore, the theory does not exclude misfolded proteins, such as Aβ and neurofibrillary tangles, as implicated in the progression of AD. Within the MR Theory, these various molecular aggregates contribute to AD pathology, in so far as they affect the mitochondrial metabolism, thus inducing energetic deficits.

Brain metabolism in AD: focus on the female brain

As stated earlier, the rationale for the MR Theory of the origin and progression of AD derives from the three main risk factors associated with the disease: age, sex, and genetics (e.g., *APOE4* polymorphism). Epidemiological studies showed that women represent two-thirds of patients with AD [46] (Box 2). Women appear to be more vulnerable to metabolic changes because they experience a drastic drop in sex hormones (at menopause) known to regulate energetic metabolism.

Recent studies support the role of the loss of protective sex hormones at the menopause as a trigger for metabolic disturbances in the female brain, thus increasing the risk of women developing AD (reviewed in [9]). The MR Theory brings a novel interpretation about sex differences observed among patients with AD because it appeals to this metabolic rationale to explain the origin of AD in women.

The sudden drop of sex hormones at the menopause, namely estrogen and progesterone, appears to impact brain metabolic activity and reduction/oxidation (redox) status given that: (i) 17β-estradiol, the main estrogen produced not only by peripheral glands (ovaries), but also within the nervous system, modulates the glycolysis, tricyclic acid cycle, and mitochondrial respiration [9,47]; and (ii) decrease in sex hormone levels is paralleled by an increase of oxidative stress in female brains [9]. Of note, before the menopause, women present higher antioxidant defenses and lower oxidative stress compared with men, probably due to the protective effects of estrogen.

In postmenopausal women, brain glucose metabolism correlates with cerebrospinal fluid estrogen levels [48], highlighting the important role of this hormone in the regulation of brain energetics. Mosconi and coworkers investigated brain glucose metabolism and cytochrome c oxidase (COX, involved in OxPhos) activity in platelets of clinically and cognitively normal women at different neuroendocrine transition stages: premenopause, perimenopause, and postmenopause [49]. Reduced glucose metabolism was observed in both peri- and postmenopausal women compared with premenopausal women, and correlated with peripheral COX activity. The gradient of abnormalities was most pronounced after the menopause, intermediate at the perimenopause, and lowest in premenopausal women. Of note, COX activity was measured in the platelets and, to our knowledge, no studies have compared OxPhos activity/gene expression in female brains

Box 2. Women, reproductive history, and Alzheimer's disease

Numerous cases of AD are clinically diagnosed among women in the USA and Europe (about 60% of all cases) annually. After 80 years of age, this significant difference between the AD incidence rate in men and women was confirmed by a recent large study including 16 926 subjects over 65 years of age with no dementia, AD dementia, and non-AD dementia [72]. Women carrying an APOE4 allele have an increased risk of developing AD earlier compared with male carriers [73]. After 85 years, incidence rates of dementia and AD were statistically greater in women than in men [72], but observational studies report AD before the age of 80 years. Recent work revealed that women may be underdiagnosed on early signs of AD, given that they perform better on verbal tests than do men [58]. In a study including 453 women and 532 men (healthy or with MCI) who took a verbal memory test, the score of each participant was compared to typical average scores for men or women. By normalizing individual scores on the sex-specific average, age, and education level, 10% fewer men and 10% more women had a diagnosis of MCI [58]. Thus, the female advantage on the verbal memory tests may mask early signs of AD, therefore delaying the diagnosis. Interestingly, women with MCI present more diffuse and spread out Tau pathology than do men [74], suggesting that more brain areas are affected in women than in men. The prevailing explanation for the sex difference in AD proposes that women live longer on average. However, increasing evidence indicates a 'biological underpinning', including a detrimental effect of the drop in sex hormones at menopause.

It is now clear that women experience drastic changes in brain metabolism at critical periods of their life, namely at menopause [59]. Recent studies highlighted a link between reproductive history and dementia risk [75–77] (Table I). Women with a longer reproductive span appear to have a lower AD risk [75]. Not only pregnancy, but also maternal breastfeeding duration appear to confer protection against AD [75,77,78]. This is thought to be due not only to sex hormone exposure over their lifetime, but also to changes in the immune system during pregnancy [75–77].

Strikingly, the age of menopause appears to correspond to the initiation of the 'prodromal phase' of AD, which usually starts 15–20 years before the appearance of the first clinical symptoms [49,79,80].

Table I. Changes in sex hormone levels and brain glucose metabolism throughout the reproductive life of women[a]

Reproductive life stage	Hormonal changes	Changes in brain glucose metabolism	Potential link with AD risk
Puberty	Increase in sex hormone levels [92]: estrogen: 15–35 pg/ml; progesterone: 0–6 ng/ml	Increase in brain glucose uptake during puberty [93]	Early puberty related with lower AD risk [5]
Adulthood	Average sex hormone levels [94]: cycling estrogen: 30–400 pg/ml; cycling progesterone: 0.1–25 ng/ml	Glucose metabolism fluctuates in different regions of the brain according to phase of menstrual cycle (i.e., midfollicular phase: relatively low estrogen and progesterone levels; midluteal phase: relatively high estrogen and progesterone levels) [95]	Women with longer reproductive span have a lower AD risk [5]
Pregnancy	Peak in sex hormone levels [96]: estrogen: 5500–30 000 pg/ml; progesterone: 100–200 ng/ml	Human data not available due to risk of FDG-PET-related radiation exposure during pregnancy. Given the increase in brain plasticity observed in maternal brains (e.g., brain adaptation for mother–infant bonding), an increase in brain glucose metabolism is expected to fulfil the new brain energy needs during this period [97]	Women with more cumulative months of pregnancy have lower AD risk [75–77]
Postmenopause	Drop in sex hormone levels [98]: estrogen: <30 pg/ml; progesterone: 0.1–1 ng/ml	Decrease in brain glucose consumption; switch to alternative energy fuel (e.g., ketone bodies and fatty acids) [59].	Late menopause related to lower AD risk [5]

[a]Abbreviation: FDG-PET: [18F] fluorodeoxyglucose positron emissions tomography.

at these different endocrine transition stages. Further clinical and/or postmortem investigations are needed to clearly identify metabolic changes occurring during this critical period, given that the study of sex differences in brain energetics is understudied and underestimated (see Outstanding questions). More recently, the same group examined brain glucose metabolism in cognitively normal participants [85 women (53 ± 6 years) and 36 men (52 ± 8 years)] [50]. They showed that women presented lower glucose metabolism compared with men. Menopausal status was the main predictor of bioenergetic differences. Interestingly, women taking hormone replacement therapy (HRT) showed higher brain glucose uptake compared with non-HRT users, whereas women who had had a hysterectomy showed trends toward lower glucose uptake. This study highlights again the importance of sex hormones in the regulation of brain bioenergetics in women, and the consequences of hormonal loss after the menopause.

Brain bioenergetics was also investigated in female rats during reproductive senescence, which is also characterized by three stages [51,52]: (i) regular estrus cycle (2–9-month-old rats); (ii) irregular estrus cycle (7–12-month-old rats); and (iii) acyclic estrus cycle (9–19-month-old rats). A down-regulation of bioenergetic-related genes was observed in the hippocampus of old acyclic females compared with young (regular) females. Interestingly, some genes (including OxPhos genes) were upregulated in younger acyclic females (9–10-months old) compared with irregular females and old (16-months old) acyclic females. As stated by the authors, these data may highlight a compensatory response that results in a shift in the brain energy metabolism that includes substrate utilization (e.g., shift to ketone bodies and amino acid metabolism) and mitochondrial function. Interestingly, this bioenergetics phenotype is also observed early in the brain of 3xTgAD mice (3-month-old females), in which increased expression of proteins involved in mitochondrial β-oxidation of long-chain fatty acids to generate acetyl-CoA, as well as conversion of ketone bodies into acetyl-CoA, was measured [53]. This indicates an early activation of ketolytic and/or fatty acid oxidation pathways to compensate for mitochondrial dysfunction and to provide alternative energetic substrates [54]. In other AD transgenic models, namely Tg2576 and APP/PS1, an increase in brain glucose uptake (hypermetabolism) was also measured in the hippocampus, cortex, and striatum of 7-month-old and 6–12-month-old females, respectively [14,16]. This may again depict compensatory mechanism aiming to fulfill energy needs of neurons with defective mitochondrial function. Of note, this hypermetabolism appears to occur at the onset of reproductive senescence in female mice [53]. In line with this, dynamic metabolic changes in female rat brains during chronological and endocrinal aging were recently described [52]. Namely, perimenopausal females presented an up-regulation in amino acid metabolism to compensate for the decline in glucose metabolism and OxPhos. The use of this interim alternative energy substrate was then followed by activation of fatty acid metabolism, which was predominant in postmenopausal females. These data further highlight a window of opportunity for therapeutic intervention. Strikingly, this study also highlights the involvement of two main AD risk factors, age and sex, in the metabolic shift observed in female brains at the menopause.

These findings suggest that women are more prone to develop AD due to the drastic metabolic changes occurring during the critical period of perimenopause. In the context of the MR Theory, one can hypothesize that the loss of female sex hormones is the cause of the following chronological events highlighted by the MR Theory (Figure 2): (i) a hypermetabolic phase at the perimenopause: upregulation of mitochondrial OxPhos (the inverse Warburg effect) in subsets of neurons in female brains. This would be a compensatory mechanism to maintain adequate production of energy and to mitigate the deficit induced by the mitochondrial dysfunction caused by the loss of regulatory sex hormones; (ii) a (quasi)-stable metabolic phase at the 'early' post-menopause, with an activation of alternative energetic pathways and the use of alternative energetic substrates (e.g., ketone bodies, fatty acids, and amino acids). The competition between

intact and abnormal (upregulated OxPhos) cells for energy substrates would result in a new bioenergetic equilibrium. This stage would correspond to AD prodromal phase or MCI; and (iii) a hypometabolic phase at the 'late' postmenopause: the collapse of the bioenergetic equilibrium due to a change in the neuronal environment and the concomitant selective advantage of hypermetabolic neurons may lead to the death of neurons with normal OxPhos and progression toward AD.

More preclinical and clinical investigations are now needed to identify and understand more precisely these bioenergetic changes that may highlight specific metabolic biomarkers.

Diagnostic programs and therapeutic strategies for women

Diagnostic programs

Diagnostic programs will necessarily involve methods for recognizing the early hypermetabolic stage of the disease.

Traditional methods can be used, namely metabolic imaging techniques, such as positron emission tomography (PET) detecting the radioactive glucose analog 2-18F-fluoro-2-deoxy-d-glucose (18-FDG). More precise tools are now available, such as deuterium metabolic imaging (DMI), which allows the generation of 3D metabolic maps revealing glucose metabolism beyond mere uptake [55]. Strikingly, DMI enabled visualizing the Warburg effect in a patient with a glioblastoma multiform brain tumor after oral [6,6′-$^{2}H_{2}$]glucose intake. This powerful tool may be an asset in the detection of metabolic changes (e.g., inverse Warburg effect) occurring during early stages of AD.

Functional magnetic resonance imaging (fMRI) also provides methods to investigate the neural underpinnings of cognitive function by measuring the regional hemodynamic changes related to cellular activities. There is a correlation between brain energy metabolism and fMRI activity [56]. Accordingly, fMRI activity should provide an index of the changes in OxPhos activity that the MR theory predicts. Indeed, according to Sperling *et al.* [57], there are three phases of fMRI dynamics: (i) an increase in fMRI activity in the early prodromal phase of AD; (ii) a stable fMRI activity that is correlated with the incidence and length of the prodromal phase; and (iii) a decline in fMRI activity in individuals with clinically diagnosed AD. These changes provide qualitative support for the MR Theory.

The existence of a hypermetabolic state suggests a new mode of diagnosing AD by detecting changes in metabolic activity in certain areas of the brain, namely the cortical neurons. Diagnostic strategies will depend on the bioenergetic changes that occur to compensate for the metabolic deficits induced by mitochondrial dysregulation caused by hormonal loss.

Therefore, the diagnostic program implies that every woman should be regularly screened (e.g., every 2 years) after the age of 40 years (premenopause) using the above-mentioned methods (Figure 2). When changes in the levels of sex hormones (translated by irregular menstrual cycles) as well as changes in metabolic activity in certain areas of the brain are detected, therapeutic strategies can be considered. Of note, similar diagnostic programs are already implemented for other diseases, such as breast cancer, whereby women are screened before any symptom appears using different screening tools, including clinical examinations and mammography.

Regarding cognitive tests, sex-specific diagnostic criteria must be applied. Indeed, women appear to perform better on verbal memory tests compared with men [58]. This point has to be taken into account to improve diagnostic accuracy. Interestingly, memory tests, including immediate and delayed recall of a paragraph, and immediate and delayed recall of paired associates,

have already been used to compare the cognitive performance of pre-, peri-, and postmenopausal women [49]. When compared with a premenopausal group, postmenopausal women showed lower memory scores on immediate and delayed recall of a paragraph, as well as on delayed recall of paired associates. A trend toward lower delayed recall of a paragraph scores was also observed in postmenopausal women compared with perimenopausal women. Therefore, these tests are good candidates to be included in the proposed diagnostic program.

Therapeutic strategies

Therapeutic strategies will necessarily involve metabolic interventions to: (i) maintain the homeostatic phase and thereby prevent the shift to the pathological phase; and (ii) regulate the rate of neurological decline once the pathological state has been attained.

The MR Theory proposes two modes of intervention against AD: (i) preventing the disease: this means metabolic interferences that will maintain the neurons in a condition described by metabolic homeostasis; and (ii) retarding the progression of the disease: This strategy involves intervention that will reduce the rate at which neurodegeneration proceeds.

Disease prevention

AD requires strategies to maintain the relative frequency of Type 1 neurons (with upregulated OxPhos) and Type 2 neurons (with normal OxPhos). This can be achieved by interventions that maintain the relative metabolic rate of both Type 1 and Type 2 neurons.

Given that the loss of female sex hormones is associated with many perimenopausal symptoms and impairments, including changes in brain metabolism [59], compensating this loss by a HRT appears to be the most logical disease prevention strategy. Indeed, it has been shown that estradiol, the main female sex hormone, regulates glycolysis, mitochondrial respiration, and reduction/oxidation homeostasis [47,60,61]. Research has also revealed that estradiol enhances energetic pathways sustaining the use of glucose as the primary fuel source for the brain [47]. In the context of the MR Theory, estradiol appears to be an excellent candidate to maintain the metabolic equilibrium between Type 1 and Type 2 neurons. Therefore, as a preventive strategy against AD, we propose that perimenopausal women (with irregular menstrual cycles), are treated with HRT comprising 17β-estradiol administration, complemented with cyclic progesterone (Figure 2 and Box 3).

Disease retardation

In AD, the neurodegeneration process has already been initiated due to the collapse of metabolic homeostasis. Type 1 neurons now have a selective advantage, a condition achieved by the change in the neuronal environment that an insult (e.g., vascular lesion) has induced. Therefore, reducing the selective advantage of Type 1 neurons may slow disease progression. This can be achieved by increasing the concentration of energetic substrates that will transform the neuronal environment from a scarce to an abundant condition, thereby enhancing the selective advantage of Type 2 neurons.

Cunnane and colleagues recently described in detail therapeutic strategies against age-related neurodegenerative disorders, based on approaches preserving, improving, or rescuing brain bioenergetics [62]. Such therapeutic approaches include the use of ketone bodies and fatty acids, which represent alternative bioenergetic substrates. Interestingly, Roberta Brinton and her group provided the first evidence linking reproductive senescence in female mice with white matter degeneration [63]. They showed activation of the catabolism of myelin lipids to generate ketone bodies, paralleled by an increase in fatty acids and mitochondrial fatty acid metabolism

Box 3. Reconsidering hormone replacement therapy to prevent AD

From a clinical point of view, the role of HRT and its benefits for women health have been debated for several decades and are well reviewed elsewhere [81]. In brief, early observational data from the 1990s showed many benefits of HRT on women's health, including reduced osteoporosis, coronary heart disease, and mortality, as well as risk of AD [82–84]. However, these beneficial effects of HRT were challenged by results from the 'Woman's Health Initiative Memory Study' (WHIMS) [85]. Data obtained from 4532 postmenopausal women aged over 68 years revealed a twofold increase in dementia after 4.2 years of HRT [conjugated equine estrogen (CCE) and medroxyprogesterone (MPA)]. The failure of the WHIMS is thought to be due to: the synthetic nature of the hormones used in the study (CCE and MPA). Indeed, protective effects of estrogen are antagonized by continuous progesterone and MPA [86]. However, progesterone is necessary to prevent the risk of developing uterine or breast cancers that a treatment with estradiol alone may induce. Interestingly, cyclic progesterone administration (following the cyclic nature of female sex hormones) in co-treatment with estradiol showed beneficial effects against AD pathology in 3xTgAD female mice [87]. Therefore, the use of a cyclic treatment regime should be also considered in women; and (ii) the age of the participants (>65 years). This point is clearly corroborated by animal studies showing an age and timing effect of HRT that benefits only younger animals [88]. These findings suggested that long-term estradiol depletion induces a decrease in the expression of the estrogen receptor, decreasing the efficacy of estradiol treatment with time. This 'timing hypothesis for HRT' has now been highlighted in several clinical studies, and outcomes of the benefits of HRT show that the treatment should be initiated in young women as soon as the sex hormone level starts dropping [89].

Strikingly, the MR Theory offers further explanations about the failure of the WHIMS and the 'critical window hypothesis' for HRT. Indeed, a HRT with estradiol initiated at the perimenopause when endogenous sex hormones decline may maintain the fragile equilibrium between Type 1 and Type 2 neurons by regulating the energy homeostasis and the reduction-oxidation state. Once this equilibrium is compromised, or if HRT is initiated too late (postmenopause), the treatment may be inefficient in preserving neuronal integrity, and may not prevent the metabolic collapse. Therefore, other therapeutic strategies may need to be implemented (see Disease retardation section in the main text).

machinery. Given that white matter degeneration is also a pathological hallmark of AD, they suggested that activation of myelin catabolism is an adaptive survival response to provide myelin-derived fatty acids as a substrate for ketone body generation to fuel an energetically compromised brain.

Preclinical and clinical studies showed that a ketogenic diet has beneficial effects on AD-related cognitive decline. A modified ketogenic diet was well tolerated, improved the metabolic health and AD cerebrospinal fluid biomarker profile of participants, as well as increasing ketone metabolism in the brain [64]. Ketone bodies also improved several cognitive outcomes in MCI and in very early AD [62,65,66].

Given that activation of fatty acid metabolism was recently shown in the brain of 'postmenopausal' female rats to counteract the decrease in glucose metabolism [52], fatty acids may also be alternative energy substrates. Omega-3 fatty acid supplementation or consumption (e.g., in fish), and dietary intervention including fatty acids, showed promising results in slowing age-related cognitive decline [67,68]. Multinutrient supplementation, including omega-3 polyunsaturated fatty acids, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and phosphatidylserine (a phospholipid) for 6 months, improved cognition and mobility in postmenopausal women (60–84 years of age) [68].

Therefore, dietary intervention aiming at supplying the brain with alternative energy sources (i.e., ketone bodies and fatty acids) appears to be beneficial to slow AD-related cognitive decline, and may be implemented in addition to HRT. According to the MR Theory, bringing more energy fuel to the brain will facilitate the maintenance of equilibrium between Type 1 (high OxPhos) and Type 2 (normal OxPhos) neurons. This bioenergetic stability may prevent or delay the metabolic collapse leading to the death of Type 2 neurons. Again, the timing of this dietary intervention is paramount, because once a rapid decline in neuronal bioenergetics is initiated (due to a change in the

neuronal environment), degeneration of Type 2 neurons will increase, leading to cognitive deficits and dementia.

Concluding remarks

The MR Theory is unique in terms of its bioenergetic explanation of the three stages (hypermetabolism, quasi-stable metabolic phase, and hypometabolism) that define the transition to AD. We have used this metabolic rationale for the origin of AD to propose diagnostic measures and sex-specific therapeutic strategies. We specifically emphasize the brain metabolic changes experienced by women over the course of the menopause, which may explain the higher incidence of AD. We furthermore exploit the theory to propose a new class of diagnostic criteria for women. According to the MR Theory, the prevention and/or retardation of AD is possible by means of programmed HRT as well as administration of substrates (e.g., ketone bodies) to recouple the availability of energetics substrates with the neuronal bioenergetics system. The accuracy of the diagnostic program in detecting early stages of AD as well as the extent of the efficacy of therapeutic strategies to prevent and/or delay AD remain to be determined experimentally (see Outstanding questions).

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Declaration of interests

None declared by authors.

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Outstanding questions

The Amyloid Cascade Hypothesis dominates the AD research field. A wealth of evidence supports that neurodegenerative processes set in motion in AD result from synergistic activities of risk factors, including genetic, environmental, vascular, and metabolic factors. A monocausal treatment (e.g., anti-Aβ therapy) will probably not cure this complex disease because the pathological constructs are too simplistic in this case. Other leads should be urgently explored, including those considering AD as a metabolic disorder.

Despite the experimental evidence raised in this Opinion, current literature regarding the inverse Warburg effect is still unidentified as such. Studies are required to clearly highlight this phenomenon and to understand the underlying molecular mechanisms.

The characterization of the mitochondrial and/or bioenergetic state at different menopausal stages in the brain is necessary because it may highlight specific metabolic biomarkers for the early detection of AD in women. New techniques, such as DMI, may be useful to draw a 3D metabolic map of the female brain at pre-, peri-, and postmenopause.

The feasibility of the diagnostic program proposed here, its costs, as well as its efficacy in detecting early stages of AD in women remain to be determined.

According to the MR Theory, the prevention of AD would be possible with a HRT (using the natural sex hormones 17β-estradiol and progesterone) at the early menopause. This would prevent the hypermetabolic stage described in this report, by preventing mitochondrial impairments caused by the loss of sex hormones. The retardation of the disease (prolongation of the prodromal stage) would be possible by providing alternative energy substrates to the brain, therefore preventing the metabolic collapse caused by the death of Type 2 (normal OxPhos) neurons. However, experimental data are necessary to confirm these proposals.

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