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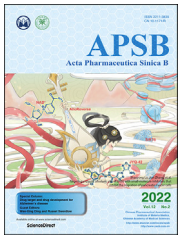

REVIEW

Targeting whole body metabolism and mitochondrial bioenergetics in the drug development for Alzheimer's disease

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Abstract Aging is by far the most prominent risk factor for Alzheimer's disease (AD), and both aging and AD are associated with apparent metabolic alterations. As developing effective therapeutic interventions to treat AD is clearly in urgent need, the impact of modulating whole-body and intracellular metabolism in preclinical models and in human patients, on disease pathogenesis, have been explored. There is

Abbreviations: αkG, alpha-ketoglutarate; Aβ, amyloid β; AD, Alzheimer's disease; ADP, adenosine diphosphate; ADRD, AD-related dementias; ACE2, angiotensin I converting enzyme (peptidyl-dipeptidase A) 2; cAMP, cyclic adenosine monophosphate; cGAS, cyclic GMP/AMP synthase; CSF, cerebrospinal fluid; DAMPs, damage-associated molecular patterns; ER, estrogen receptor; ETC, electron transport chain; FCCP, trifluoromethoxy carbonylcyanide phenylhydrazone; PET, fluorodeoxyglucose (FDG)-positron emission tomography; FPR-1, formyl peptide receptor 1; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HBP, hexoamine biosynthesis pathway; HTRA, high temperature requirement A; hAPP, human amyloid precursor protein; hPREP, human presequence protease; I3A, indole-3-carboxaldehyde; IRF-3, interferon regulatory factor 3; i.p., intraperitoneal; LC3, microtubule associated protein light chain 3; LRR, leucine-rich repeat; LPS, lipopolysaccharide; MCI, mild cognitive impairment; MAVS, mitochondrial anti-viral signaling; Mdivi-1, mitochondrial division inhibitor 1; mtDNA, mitochondrial DNA; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; mTOR, mechanistic target of rapamycin; NeuN, neuronal nuclear protein; NLRP3, leucine-rich repeat (LRR)-containing protein (NLR)-like receptor family pyrin domain containing 3; NOD, nucleotide-binding oligomerization domain; PKA, protein kinase A; POLβ, the base-excision repair enzyme DNA polymerase β; ROS, reactive oxygen species; SAMP8, senescence-accelerated mice; SCFAs, short-chain fatty acids; SIRT3, NAD-dependent deacetylase sirtuin-3; SkQ1, plastoquinonyldecyltriphenylphosphonium; STING, stimulator of interferon genes; STZ, streptozotocin; T2D, type 2 diabetes; TCA, Tricarboxylic acid; TLR9, toll-like receptor 9; TP, tricyclic pyrone; TRF, time-restricted feeding; TMAO, trimethylamine *N*-oxide.

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Hexokinase biosynthesis pathway;
Diabetes;
Circadian regulation;
Microbiome

also an increasing awareness of differential risk and potential targeting strategies related to biological sex, microbiome, and circadian regulation. As a major part of intracellular metabolism, mitochondrial bioenergetics, mitochondrial quality-control mechanisms, and mitochondria-linked inflammatory responses have been considered for AD therapeutic interventions. This review summarizes and highlights these efforts.

1. Introduction

Alzheimer's disease (AD) is an age-dependent progressive neurodegenerative disorder and the most common cause of dementia. Pathologically, AD postmortem brains exhibit protein aggregation, mitochondrial dysfunction, and neuroinflammation[1,2]. Many studies have indicated that aging is the greatest risk factor for most chronic, non-communicable diseases, including AD. Specifically, the per capita death rate from AD at ages 75−85 is 70 times higher than at ages 55−65, and 700 times higher than at ages 45−55[3]. Metabolic perturbations have been linked to AD both in the whole body and at the cellular level in the brain[1]. Indeed, impaired insulin sensitivity is observed in the majority of people 65 years old or older[4], and type two diabetes (T2D) increases the risk of AD[5−7]. Epidemiology studies as well as investigations of clinical manifestations and mechanisms indicate common links between diabetes and AD[5−13]. While metabolic pathways contributing to energy production are essential for normal neuronal function, decreased glucose metabolism occurs in AD brains[7,9,10]. In rodent models that recapitulate aspects of AD, for example, APP/PS1 mice, impaired glucose tolerance and insulin sensitivity have been observed[14]. Streptozotocin (STZ) not only induces diabetes by disrupting pancreatic β cell function, but also affects learning/memory and exacerbates pathology in AD models[15,16]. Although the molecular mechanisms that underlie the connection between AD and diabetes are not yet clear[17,18], these observations led to the idea that anti-diabetic drugs may have benefit in AD[18−21]. Regulation of glucose metabolism including glycolysis and the hexosamine biosynthesis pathway have also been discussed in the context of AD pathogenesis and as the basis of intervention strategies[22−26].

Glycolysis and mitochondrial energy production are closely linked in nearly all cell types and tissues, and together they contribute to whole body and cellular metabolism. Perturbation of glucose metabolism and mitochondrial dysfunction are a common feature of both diabetes and AD[6−13,27]. It is clear that mitochondrial DNA mutations, deficiencies in electron transport chain activities, and deficits in glucose and lipid metabolism take place in AD[28−35]. The "mitochondrial cascade hypothesis"[33,36−38] has proposed that mitochondrial dysfunction plays an important role in the etiology of AD. Because of the crucial role of mitochondria in bioenergetics, metabolites homeostasis, electron transport chain related redox signaling, and neuroinflammation phenotypes, targeting the mitochondrial function, homeostasis, and mitochondrial quality-control mechanisms has emerged as a therapeutic strategy for age-related neurodegenerative diseases, including AD[27,34,35,37,39−53]. This review will summarize and highlight recent efforts to target metabolism and mitochondrial function, as well as inflammation, as a strategy for AD therapy. With the recent increasing awareness of sex differences, microbiome, and circadian regulation of metabolism, we will also discuss renewed interest in targeting these pathways.

2. Whole-organism energetics and potential targets for AD therapeutics

2.1. Glucose metabolism and insulin signaling

Multiple clinical observations have revealed a relationship between AD and AD-related dementias (ADRD) and energy balance. Energy balance is most simply defined in biological systems as the difference between energy intake (dietary calories) and energy expenditure (metabolic rate) over a set period of time[54]. These energetic imbalances are representative of both systemic and localized changes in metabolism within the body. Both obesity and weight loss have been suggested to be risk factors or signs of AD development[55−57]. Mid-life obesity has generally been associated with earlier onset and severity of AD/ADRD (albeit with exception)[58−60]. Energy imbalance as observed with weight loss in midlife or late life is associated with increased dementia risk[61−63]. Thus the contribution of energy imbalance to AD onset or progression and the complexity of the relationship based on the timing of the energy balance assessment (pre-*versus* post-AD diagnosis) need to be fully understood; similarly, clinical studies may need to consider both BMI and energy balance in their design (Fig. 1)[64,65].

Multiple methods have been used to perform energy-expenditure assessments following AD diagnosis. Studies that used the doubly labeled water technique for daily energy expenditure and measurements of body composition *via* dual-energy X-ray absorptiometry in subjects with and without AD revealed that, in older subjects with AD (~70 years of age), daily energy expenditure was significantly lower than in healthy controls (~14% lower), as were levels of physical activity. However, this difference in energy expenditure was representative of the difference in body composition between the groups[66,67], resulting in no difference in energy expenditure when included in the statistical models. In contrast, resting energy expenditure measured by indirect calorimetry is reported to be either slightly elevated or to have no significant difference with AD[68,69]. Assessments of energy intake have generally reported no differences between subjects with and without AD, thus raising further questions regarding the temporal pattern of weight loss and energy expenditure. These results contrast with multiple pre-clinical models of AD where a hypermetabolic state has been shown with elevated food intake but decreased body weight gain, reflective of elevated energy expenditure[70,71].

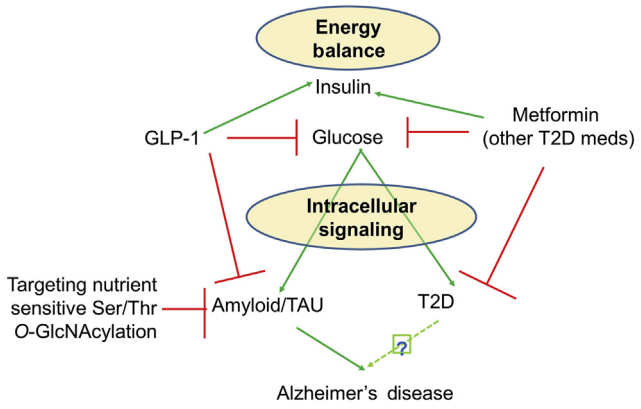

Figure 1 Relationships among energy balance, insulin/glucose, intracellular insulin signaling, targeting protein Ser/Thr *O*-GlcNAcylation, type two diabetes (T2D), and AD risk. Green arrows indicate "stimulation" and red lines "inhibition".

Alongside whole-body measures of energy expenditure, tissue-specific and substrate-specific metabolism have been measured in multiple AD models and clinical states. Pre-clinical models of both diabetic and non-diabetic rats with increased β-amyloid exposure in the hippocampus show significant decreases in energy intake, activity, and fat oxidation but increases in carbohydrate oxidation and energy expenditure (resulting in negative energy balance and weight loss)[72]. Assessments of *in vivo* metabolism through various indirect methods have shown that, in patients with AD, cerebrospinal fluid (CSF) concentrations of lactate and pyruvate were higher, while succinate, fumarate, and glutamine were lower than controls, suggesting an impairment of mitochondrial oxidative metabolism of glucose[73–75]. A proposed deficit in cerebral glucose metabolism is further confirmed by *in vivo* imaging [*e.g.*, FDG-PET and magnetic resonance imaging (MRI)] of tissue atrophy and lower glucose metabolism, including specific metabolic deficits in the precuneus, posterior cingulate, and temporal-parietal, as well as the hippocampus and default mode network brain regions, which vary by age at onset and disease progression[74,76–81]. Complementary methodologies using magnetic resonance spectroscopy measures of glucose and related metabolite levels in brains of subjects with AD support a reduced glucose metabolism, including elevations in the glucose:creatine ratio[82,83].

These systemic and localized deficits of carbohydrate metabolism are reminiscent of known risk factors for AD, which include both T2D and metabolic syndrome[84,85]. While a unified model of insulin resistance in contribution to AD onset or progression is yet to be fully verified, hyperglycemia and insulin resistance appear to precede and have predictive significance for AD-related biomarkers in both pre-clinical and clinical studies[16,86–88]. Cellular defects related to the metabolic stress present with both T2D and metabolic syndrome highlight the significance of insulin and insulin-like growth factor in peripheral and central metabolism, with further focus being placed on cell-specific insulin sensitivity in cerebral tissues[86,89,90]. Whether and how insulin sensitivity itself or in combination with pathological alterations accompanying insulin resistance (*e.g.*, lipid metabolism, inflammation, misfolded protein stress, oxidative stress) contribute to AD risk and development remain to be fully dissected. However, a growing body of evidence suggests that targeting insulin resistance may have beneficial or protective effects despite a lack of clarity regarding the underlying mechanisms[19,20].

One of the most-used diabetes drugs is metformin, which improves insulin sensitivity with effects including but not limited to the increasing peripheral uptake of glucose and suppression of hepatic glucose production[91]. Metformin's potential beneficial effect in AD is being explored[92,93]. An ongoing clinical trial NCT03733132 (double-blind, placebo-controlled, randomized design) will recruit 40 participants (>65 years with fasting glucose between 100 and 140 mg/dL and abdominal girth of >102 cm in men and >88 cm in women) to determine brain ATP production by ^{31}P-MRS, brain structure and blood flow by functional MRI, muscle mitochondrial respiration, and cognitive function, after 40 weeks of metformin. This study may help provide evidence of the effects of metformin on cognition and bioenergetic function. As will be discussed later in "Section 3 Targeting mitochondrial bioenergetics and mitochondrial quality control", the effect of metformin on mitochondrial complex I activity was demonstrated first in 2000 in permeabilized hepatocytes and isolated mitochondria[94,95] and then reported in many other cell types. Note that high concentrations of metformin have been used in these studies, and a lower concentration was found to be required to activate AMPK and inhibit mitochondrial glycerophosphate dehydrogenase[96]. Whether metformin's inhibition of mitochondrial complex I is a prerequisite for its beneficial effects for diabetes or AD is still being debated.

Based on the observation that insulin signaling can regulate second messengers including AKT and MTOR[97], and that perturbation of insulin signaling occurs in AD patient brains[18], insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists have been used in animal models to test their effects on AD-related phenotypes. In clinical trials for mild cognitive impairment (MCI)/AD patients, nasal delivery of insulin was used, since systemic administration of insulin may lower blood sugar levels in people who are not diabetic. In non-AD young adults, 8 weeks of intranasal administration of insulin improved memory and mood in a double-blind, between-subject comparison[98]. Memory improvement was later found to occur in memory-impaired older adults and early AD patients[99–101] and was also shown in several pilot clinical trials[102]. Because larger scale clinical trials have had mixed results, there is still a need for further investigations on if there are yet unknown factors that influence the outcome of intranasal insulin administration[103,104].

In addition to insulin, other diabetic drugs that modulate insulin signaling have been tested in animal models of AD. Daily intraperitoneal (i.p.) injection for 8 weeks of the GLP-1 analogue liraglutide in APP/PS1 mice has been shown to decrease β-amyloid plaque, decrease numbers of activated microglia, increase dentate gyrus young neurons, and improve synaptic plasticity[105]. A 12-month multicenter, randomized, double-blind, placebo-controlled phase IIb trial is ongoing with 206 patients[106]. In addition, dual GLP-1/GIP receptor agonists DA5-CH and DA4-JC also attenuated memory loss in APP/PS1[107]. The pancreatic hormone amylin has been targeted by using its synthetic analogue as a potential therapy for AD, perhaps due to its plaque-forming potential and its effects on cAMP and PKA signaling[108]. Neuropeptides that may increase neuronal glucose transport are also considered to be potential drug targets in AD prevention and therapy[109].

Downstream of glucose phosphorylation by hexokinase, the hexoamine biosynthesis pathway (HBP) generates *O*-GlcNAc to

enable post-translational modification of proteins on Ser/Thr residues[110]. This post-translational modification is sensitive to nutrient availability and cellular stress[26,110–117]. It has been observed that pharmacological inhibition of the enzyme that removes the *O*-GlcNAc from proteins resulted in more preserved tau *O*-GlcNAcylation, and decreased tau phosphorylation and aggregation[22,118–121]. Thus, there has been significant effort put forth to improve the brain penetration and efficacy of these pharmacological agents to aid in developing suitable potential drugs for clinical trials[22]. However, there are still concerns regarding targeting this pathway based on studies in cell culture, which demonstrated potential inhibition of autophagy[113,122,123], and in animal models, which demonstrated a potential detrimental effect on learning and memory[124]. A better understanding of the functional consequences of *O*-GlcNAc modifications of specific proteins and development of approaches to change the *O*-GlcNAcylation status of specific proteins are needed.

2.2. *The gut microbiota and AD*

AD has long been considered solely as a brain disease, with no apparent relationship to other distal tissues. This view has begun to change over the last 20 years, beginning with the Rotterdam study in 1999[125], suggesting that metabolic inflexibility (the inability to shift substrate utilization) is a major contributor to the development of AD and related pathologies. As discussed above, conceptually, there is a strong correlation of pathological mechanisms of AD and metabolic disorders such as obesity, metabolic syndrome, and diabetes, with hallmarks including dysregulated glucose homeostasis and insulin resistance[126]. This metabolic inflexibility increases with age, the greatest known risk factor for the development of AD; however, in retrospective analyses, metabolic disturbances in even relatively young individuals predict future diagnosis of AD[61,127–133].

A common link between metabolic dysregulation and AD is dysbiosis of the human intestinal tract or "gut"—commonly defined as a disturbance of or change in the density and/or composition of gut microbiota. Indeed, the human gut is inhabited by over 100 trillion microorganisms; including but not limited to over 1000 known species of bacteria[134–136]. As early as 1908[137], a link between the gut and senility was proposed, but until the last 20 years, this connection was mainly overlooked in the context of human health and disease. However, gut microorganisms encode >150 times more genes than the human genome and are highly involved in numerous metabolic reactions. Most gut bacteria can be classified as either harmless (commensal) or beneficial (symbiont), with a very few classified as pathogenic (pathobiont)[138]. Still, pathogenic bacteria are often suppressed by a healthy balance among all gut bacteria to maintain gut homeostasis[139,140].

Gut dysbiosis has been linked to a wide variety of metabolic-related diseases, including obesity and diabetes[141]. The two most dominant phyla in the human and mouse gut are Firmicutes and Bacteroides, representing more than 90% of the total bacterial community[142,143]. Many early studies suggested that metabolic conditions, including metabolic syndrome and diabetes, are associated with a lower Bacteroidetes/Firmicutes ratio[144–146]—although this measure has become more controversial in the last few years[143]. In line with this reasoning, there is growing literature demonstrating that the microbiota are critical to several functions of the central nervous system that occur in the context of AD[147], including myelination, neuroinflammation, and regulation of blood–brain barrier integrity, as well as regulation of neurogenesis and accumulation of α-synuclein[148]. This communication occurs *via* the "gut–brain axis," which includes the central nervous system, the autonomic and the enteric nervous system, and the peripheral nerves[149], to influence host health- and lifespan. Studies of the gut microbiota profile in patients with AD indicate that this profile is markedly different from that of persons without AD[150,151]. As is the case in the metabolic diseases described above, one study has shown that patients with AD showed decreased microbiota richness with a decrease in the ratio of Firmicutes to Bacteroidetes[151]. However, inconsistent results have been noted both in human patients and in animal studies, including mouse, rat, and fly models of AD[148]. Although these studies support the interaction between gut microbiota and AD pathogenesis, the reason for the discrepancy in the changed composition of gut microbiota is not clear. To be sure, levels of these two phyla depend on many things, including natural variations in host relative abundance (which may be strain and husbandry dependent in the case of preclinical studies), host diet, host physical activity levels, and potentially gut regionality changes in these bacteria. In addition, changes to the relative abundance of more pathobionts may play a larger role in both metabolic disorders and AD discussed here[145,148].

Recent studies of the contribution of bacterial metabolism and their metabolites and how they influence metabolic alterations in the host aim to explain AD pathogenesis in the context of metabolic disruption. For example, a hallmark of insulin resistance in humans is an increase in the gut-microbe-derived metabolite trimethylamine *N*-oxide (TMAO), which is also associated with several metabolic disorders[152]. Studies have shown elevated TMAO levels, correlating more with p-tau than Aβ levels, in the CSF of AD patients[153]. Bacteria-derived secondary bile acids, that are known to impact metabolic health and disease through modulation of cholesterol metabolism and clearance[154], are elevated in patients with AD compared to non-afflicted controls[155–157], associated with cognitive dysfunction—although the exact mechanism is unknown. Short-chain fatty acids (SCFAs), which are essential to lipid/protein metabolic process and influence glycemic control in a variety of metabolic conditions[158], may have a neuroprotective role in AD. This protection may occur by enhancing energy substrates to the brain or regulating microglial maturation and function[159]. Tryptophan is also known to influence metabolic health, perhaps through its downstream derivative, indole[160]. Indole derivatives can have beneficial or toxic effects, and the regulation of derivative production is dependent upon the composition of the intestinal microbiota. Meanwhile, the vast majority of tryptophan is metabolized to the neuro-regulatory kynurenine pathway—a key link between gut dysbiosis and neurodegenerative conditions including AD[161–166]. Notably, members of the genus *Lactobacilli* promote the production of indole-3-carboxaldehyde (I3A), which promotes the production of interleukin 22 and the maintenance of mucosal reactivity[167]. Mechanistically, angiotensin I converting enzyme (peptidyl-dipeptidase A) 2 (ACE2) is essential to intestinal absorption of tryptophan[168,169], regulates intestinal immune function and gut microbiota ecology, and attenuates intestinal inflammation suffered in response to epithelial damage[168–171].

How the gut microbiome affects whole-body metabolism and mitochondrial bioenergetics both in the brain and in the circulation is unclear. Whether changes to the gut microbiome are a consequence of or a contributing factor to the pathogenesis of AD still remains to be addressed. Overall, the gut–brain axis is an important integrative system that modulates metabolic balance, and hence is a potential target for managing AD (Fig. 2). Recent clinical studies found that remodeling the gut microbiome with

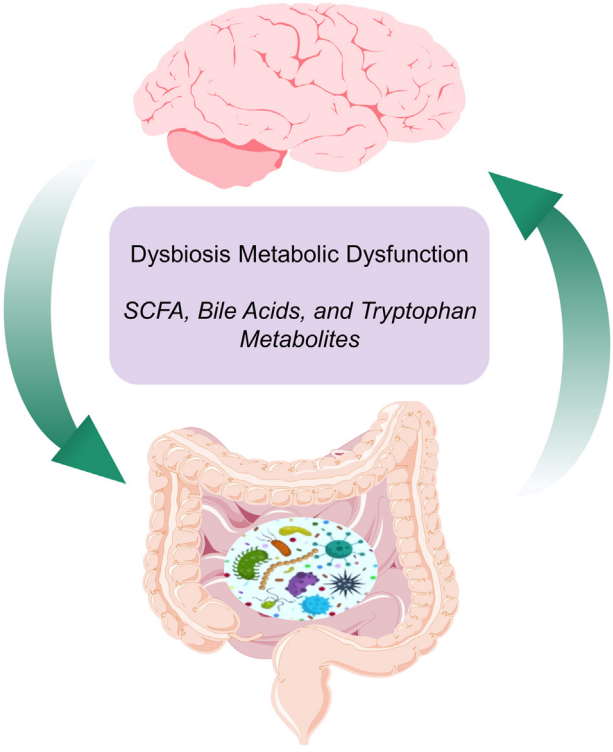

Figure 2 A common link between metabolic dysregulation and AD is dysbiosis of the human intestinal tract or "gut"—commonly defined as a disturbance of or change in the density and/or composition of gut microbiota. Bacterial metabolites (purple box), may influence metabolism to directly or indirectly impact neuronal function. Overall, the gut−brain axis (the brain affects the gut through neuronal and hormonal signals, and the gut microbiome affects the brain) is an important integrative system that modulates metabolic balance and, hence, is a potential target for managing AD.

GV-971, a sodium oligomannate, improved cognitive function in a phase III, double-blind, placebo-controlled trial with 818 mild to moderate AD patients in as little as 4 weeks, perhaps through decreasing neuroinflammation[172−176]. A small clinical trial (10 participants, ClinicalTrials.gov Identifier: NCT03856359, Bausch Health and Duke University) is being conducted to investigate the effect of rifaximin, an antibiotic that alters gut microbiota, on cognition and serum pro-inflammatory markers, as well as gut microbiota. How specific dietary modulation and pro/prebiotic supplementation affect gut microbiome as well as whole-body and neuronal energetics still needs to be critically evaluated.

2.3. Targeting circadian regulation in diabetes treatment and implication in AD

Disturbances in the sleep/wake cycle are common in the elderly and in AD patients, with fragmented nighttime sleep, increased nocturnal activity, and daytime sleepiness, which are considered among the most disruptive symptoms of AD[177−181]. Metabolism, mitochondrial function, and the cellular protein/organelle quality-control mechanisms (including autophagy and mitophagy) have all been shown to be regulated by central and peripheral circadian clocks[115,182−185]. In mouse models, disruptions of circadian-regulating transcription factors result in impaired learning and memory[186−194].

Therapeutic strategies targeting the sleep/wake cycle or the circadian clock have been explored. In a 2008 report of a trial in group care facilities that lasted more than 12 months, 189 residents were with a randomized assignment to whole-day bright versus dim light. Furthermore, they were double-blind and placebo-controlled for evening 2.5 mg melatonin. The study has shown that light treatment attenuated cognitive decline, and attenuated melatonin use was associated with withdrawn behavior[195]. In a 2014 multicenter study of 73 mild and moderate AD patients, in addition to standard therapy of acetylcholinesterase inhibitors ± memantine, patients were given a placebo for 2 weeks and then randomized to receive a placebo or 2 mg prolonged-release melatonin nightly for 24 weeks, before receiving 2 weeks of a placebo. The melatonin group had improved cognition and a similar adverse event profile as the placebo group[196]. A recent study of 37 nursing home residents 70−93 years of age treated with bright light for 90 min in the morning for 5 days also showed cognitive improvement[197]. How cognitive improvement is associated with other elements of aging in response to light and/or melatonin therapy, and whether it involves metabolic and redox-related mechanisms, will need further investigation.

Coffee consumption has been used in humans to improve alertness during day time activities; caffeine has also been reported to decrease AD risk in humans and decrease pathological and cognitive impairments in AD mouse models[198]. However, a 2018 meta-analysis found no change in risk of AD with coffee consumption[199], suggesting that the current data are insufficient as evidence of the utility of coffee consumption as an AD prevention strategy. Time-restricted feeding (TRF) is another intervention being explored for metabolite modulation, healthy aging, and potential AD therapy[184,200−203]. TRF applies the idea that restricting the daily feeding period without decreasing caloric intake by aligning feeding/fasting activities with the intrinsic and extrinsic circadian clock is better for overall health in general and for alleviating neurodegenerative disease in particular. TRF in mice changes gene expression and metabolite abundance in multiple tissues, with the most extensive studies focusing on the liver[204]. In a human study with 11 overweight adults, early TRF (8 a.m.−2 p.m.) decreased mean 24-h glucose level, increased before-breakfast ketones, cholesterol, and the expression of SIRT1 and LC3A in the white blood cells, and increased evening *MTOR* gene expression in the white blood cells, compared to the control (8 a.m.−8 p.m.)[203]. A randomized pilot study in 24 healthy people with 10 people feeding normally for 6 weeks and then feeding within 8 h/day for 6 weeks and 14 people feeding within 8 h/day for 6 weeks before normal feeding for 6 weeks did not find that TRF changed lean mass, bone density, nutrient intake, or cardiovascular function[205]. A short-term (5-day) crossover study with 8-h *versus* 15-h TRF in 11 obese people found changed lipid and amino acid metabolites in serum and muscle[200]. Patients with T2D (19 completed) in a TRF (within 9 h/day) study for 4 weeks did not find a consistent decrease in body mass or a consistent improvement of cognition, but the regimen had various barriers to adherence[206]. These studies have presented both potential benefits and challenges to using this strategy in humans.

Pharmacological reagents that target circadian-regulating transcription factors have also been explored in AD animal models. As transcriptional repressors that are part of the circadian clock, REV-ERBs have ligand-binding domains that bind heme and have been found to be regulated by synthetic agonists and antagonists[207−210]. On one hand, activation of REV-ERB by SR9009 suppressed lipopolysaccharide (LPS)-induced hippocampal neuroinflammation[211], decreased Aβ in the cortex, and

reversed cognitive dysfunction of aged SAMP8 mice[212], which seems to be consistent with the finding that loss of REV-ERBα resulted in impaired memory[193,194]. However, pharmacological inhibition of REV-ERBs (with antagonist SR8278) or knockdown of REV-ERBs has been found to accelerate microglial uptake of fibrillary Aβ and increase transcription of BMAL1[213]. Furthermore, REV-ERBα knockout decreased plaque number and size and prevented an increase in the microglial proteins TREM2, CD45, and CLEC7A in 5XFAD mice[213]. The lack of consistency between these observations may be due to the differences in the mouse models—LPS and SAMP8 models compared to 5xFAD models—or because both activation and suppression of REV-ERBs can stimulate intracellular processes, which is protective against neuroinflammation and proteotoxicity (Fig. 3).

2.4. *Sex differences and AD*

Sex differences in the incidence and progression of chronic diseases of aging, such as AD, are ubiquitous. In the United States, men die at higher age-adjusted rates from eight of the 10 top causes of death. The two exceptions are stroke, for which there is no sex difference, and AD of which women die at a consistently higher age-adjusted rate. AD is the only major cause of death from which women suffer and succumb at a higher rate than men[3]. This sex bias in AD prevalence and deaths is not confined to the U.S. Although the reported prevalence of AD varies widely across the globe, the female sex bias is reported in national vital statistics from the EU, UK, Japan, and, in fact, all countries that maintain reliable health records[214–216]. Neurodegenerative diseases more generally are either not sex biased or are biased toward men. For instance, men have substantially higher incidences of Amyloid Lateral Sclerosis, Parkinson's disease, and vascular dementia[215,217].

Almost two-thirds of people currently under clinical care for AD are women. That number is influenced by both women's greater age-independent incidence and the fact that women live longer than men. Given that men also display more of some prominent AD risk factors, such as greater prevalence of metabolic diseases, the female bias becomes even more puzzling. One intriguing hypothesis posits that survivor bias is largely responsible. That is, men at the highest risk for AD die from cardiovascular events before they can develop AD[1]. Another hypothesis relates to the educational advantage that men had for most of the 20th century. Educational attainment is a well-known protective factor for AD[218]. People of an age to be most susceptible to AD now were educated at a time when women had less access to education for a variety of reasons. As the mechanistic link between educational achievement and AD is as obscure as the pattern is clear, we will not pursue it further.

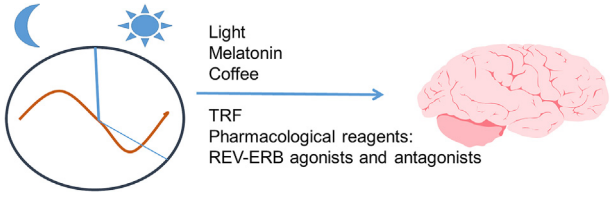

Figure 3 The circadian clock regulates metabolism and mitochondrial function in various model systems. Disturbances in the sleep/wake cycle in aging people and AD patients were prominent disruptive symptoms. Thus, restricted light, restricted food intake, and reagents that modulate the circadian clock, such as melatonin, coffee, and REV-ERB agonists and antagonists, are being considered for targeting whole-body and mitochondrial metabolism in the context of AD therapy.

Focusing on possible biological causes for women's increased susceptibility to AD, we are left with some alluring hypotheses and provocative but not compelling evidence. As alluded to previously, the evidence for some mitochondrial role in the development and progression of AD is now compelling[38]. It is the link between sex differences in mitochondrial function, and sex differences in AD, that requires clarification, as the evidence from mouse models has been complex and sometimes conflicting. There seems to be a consensus that males and females differ in mitochondrial substrate utilization, particularly under nutrient stress[219]. However, there is little consensus on anything else. This is likely due to variation among the more than 100 mouse models of AD[220] and the range of genetic backgrounds on which they are expressed. Also, most neurological sex differences are likely to be cell-type, possibly cell-compartment, and brain-region specific. For instance, AD patients showed a deficiency in the base-excision repair enzyme DNA polymerase beta (POLdβ), and that important repair enzyme was present in mitochondria in the brain, but not the liver. Other recent work observed mitochondrial complex I—specific impairment in cortical synaptic brain mitochondria in female, but not male, 3xTg mice, a common mouse model of AD[221]. On the other hand, in the same model, females, but not males, displayed enhancement of complex II-dependent respiration in non-synaptic, glial-enriched mitochondria from the cortex and hippocampus[222]. The challenges in interpretation of these complex findings are significant.

Arnold has divided mechanisms of sex differences into three categories[223]. The first category is organizational differences due to differential hormone exposure during development. Briefly, the SRY region of the Y chromosome directs testis formation in the developing embryo, and these hormones produced during fetal life have permanent structural effects on the brain. These organizational factors impact the structure, cell number, and cell types in the developing mouse brain[224]. Second, activational differences are due to the adult hormonal milieu, and they can be modulated by gonadectomy and hormone supplementation. The third is chromosomal differences, due either to genes expressed on the Y chromosome or those expressed differentially by incompletely inactivated X chromosomes. A number of genetic mouse models have been generated in order to study these categories separately[225]. One observation is that men with AD die earlier than women with AD. Using mice genetically modified to express the human amyloid precursor protein (hAPP) and to develop either testes or ovaries independent of X and Y chromosome dosage, it was shown that hAPP-XY mice died earlier and showed greater cognitive deficits regardless of whether they had testes or ovaries compared with hAPP-XX mice, regardless of whether they had testes or ovaries. In other words, an extra X chromosome was beneficial regardless of gonadal sex. Furthermore, a candidate gene, *Kdm6a*, encoding a histone demethylase, has been identified for the resilience accompanying a second X chromosome that is not inactivated[226]. It will be interesting to see whether this candidate gene bears out as a main contributor to this effect, whether it changes whole-body and mitochondrial metabolism, and whether enhancing its function or the function of its downstream targets can be of therapeutic value (Fig. 4).

We want to emphasize that, for all the wonderful biology that can be performed with genetically modified mice, there is a

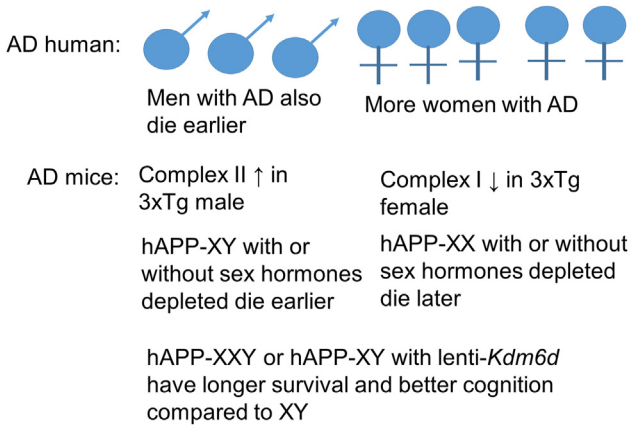

Figure 4 Currently, more women than men have AD. However, this may be due to socioeconomic or lifespan differences between men and women. It has been shown that men with AD die earlier than women with AD. Even though there is no difference in lifespan between sexes, mitochondrial complex I and II activities are different between sexes in the 3xTg AD model. In the hAPP model, the X chromosome has been shown to extend survival and enhance cognition.

possibility that this is simply not the right model with which to explore human sex differences in AD, both in terms of understanding AD pathogenesis and with regard to testing therapeutic interventions. Despite the wealth of genetically engineered mouse AD models available, there have been no therapeutic treatments that showed promise in mice and have translated to humans. Mice, unlike humans, do not have consistent differences in longevity between the sexes[227], so it is conceivable that other sex differences apparent in humans may not be replicated even in the most "humanized" mouse. Alternative models are becoming available, such as transgenic rats, which seem to replicate the human AD phenotype more closely[228].

3. Targeting mitochondrial bioenergetics and mitochondrial quality control

The major source of energy comes from the mitochondria. Furthermore, mitochondria provide key metabolites for biosynthesis and signaling molecules that sense and respond to the environment and modulate cellular function. Mitochondrial dysfunction has been proposed to play an important role in AD[36]. The link between mitochondrial and metabolic dysfunction in AD has been demonstrated with the identification of mitochondrial DNA mutations, impairment of electron transport chain activities, and deficits in glucose and lipid metabolism[28–35,229]. Both coupled (with ADP) and uncoupled (with FCCP) oxygen consumption rate in the presence of complex I substrates in freshly isolated mitochondria from the cortex and hippocampus were decreased in the 3xTg mice, earlier in females than males, and before a detectable decrease of representative proteins in the electron transport chain complexes[230,231]. In contrast to complexes I and IV[33,232], evidence for deficiencies of complex II, III, or V activities in AD were not as pronounced. Nonetheless, decreased complex II activity has been reported in the APP/PS1 mouse model[233], and levels of representative proteins of all the five electron transport chain complexes were decreased in the cortical piriform and insular regions of the 3xTg mice before the onset of detectable plaques[231]. Targeting the mitochondrial bioenergetics and quality-control mechanisms, including mitochondrial dynamics, mitochondrial movement, and mitophagy, has been increasingly explored for AD therapeutics development[34,35,37,39,40]. First, we will discuss targeting mitochondrial respiratory chains and then mitochondrial quality control (Fig. 5).

3.1. Targeting mitochondrial electron transport chain (ETC) proteins

Because of the observation that there is a decline in glucose metabolism, an obvious approach would be to attempt to supplement glucose. However, decreased glucose metabolism is not associated with decreased circulatory glucose; on the contrary, it is often associated with increased blood glucose, as with diabetes. Hence, not surprisingly, supplementation of glucose alone does not seem to be a viable strategy for AD treatment. Enhancing mitochondrial bioenergetics has been considered. Interestingly, however, inhibition of mitochondrial respiration in many cases turned out to enhance lifespan and protect against tissue damage, a phenomenon likely attributable either to decreased mitochondrial production of reactive species or to an adaptive mitohormesis response to selective stress[234–247]. For example, inhibition of ETC

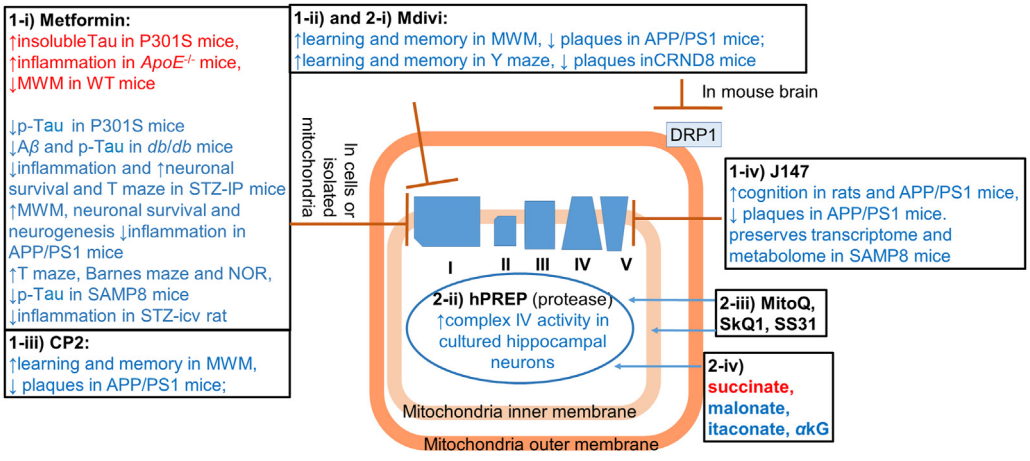

Figure 5 Compounds or peptides that target mitochondrial complex I, complex V, mitochondrial fission protein DRP1; and means to deliver mitochondrial protease, and TCA cycle substrates have been tested in preserving/improving mitochondrial function or in AD models.

complex I increased lifespan in non-mammalian species[248], and several compounds that have been found to be beneficial in animal models of AD have mild complex I inhibitory activities.

3.1.1. Metformin

As described earlier in "Section 2 Whole-organism energetics and potential targets for AD therapeutics", metformin is a compound that has been discovered to have an anti-diabetic effect and was later reported to reversibly inhibit complex I (IC_{50} ~20 mmol/L) [91,94,95,249]. In primary neurons from wildtype and human tau transgenic mice, metformin decreases tau phosphorylation, consistent with a beneficial effect[250]. However, metformin increases Aβ generation in neuroblastoma cells[251], activates AMPA/BACE1 in wildtype mice[251], increases insoluble Tau, and exacerbates hindlimb atrophy and hyperactivity in P301S Tau transgenic mice, despite the decrease in p-Tau[252]. In *ApoE*$^{-/-}$ mice, metformin treatment for 18 weeks led to increased p-Tau, decreased NeuN and PSD95 positive cells, and increased neuroinflammation[253]. In wildtype C57BL/6J mice, metformin in drinking water for 4+ weeks led to improved motor coordination but worse performance in the Morris water maze[254]. These observations argue against using it alone as a therapeutic strategy. In a study with diabetic *db*/*db* male mice, metformin administration for 4.5 months alleviated *db*/*db*-associated increase of Aβ and p-Tau, as well as *db*/*db*-associated decrease of synaptophysin, but did not change *db*/*db*-associated poor performance in Barnes maze and fear conditioning learning and memory test[255]. In mice with diabetes induced by i.p. injection of streptozotocin, metformin twice-daily gavage for 21 days improved diabetes-associated learning and memory performance on a T-maze, decreased neuroinflammation, and increased neuronal survival[256]. Metformin i.p. injection starting at 26 weeks of age for 14 days in APP/PS1 mice led to improved performance in the Morris water maze learning and memory test, decreased neuroinflammation, and increased neuronal survival and neurogenesis[257]. Metformin also decreased neuroinflammation and Aβ in APP/PS1 mice treated at 7 months of age for 8 weeks[258]. Daily injection of metformin to the senescence-accelerated mice (SAMP8) starting at 11 months of age for 8 weeks led to improved performance in the T-maze, novel object recognition, and Barnes maze and decreased p-Tau[259]. In rats with intracerebroventricular injection of streptozotocin, metformin administration improved neuroinflammation and cognition both *via* oral gavage[260] and *via* nanoliposomes[261]. In mice 8−10 months of age, daily i.p. injection of metformin for 14 days increased neurogenesis, and 3xTg mice of similar age and treatment had improved learning and memory, as assessed by the Morris water maze test[262]. Thus, despite its use in diabetes patients and the idea that diabetes and AD share several common mechanisms, including perturbation of insulin signaling, in rodents, metformin's effects on neuropathology and cognition vary with the specific animal model[263,264]. Furthermore, the effects of metformin administration on mitochondrial bioenergetics *in vivo* in AD models have not been thoroughly investigated.

Epidemiological data regarding metformin's positive effect on cognition is also mixed, likely due to the diversity of the clinical populations[263−265]. In a recent meta-analysis of 10 studies, it was concluded that metformin significantly decreased cognitive deficits in patients with T2D, and significant improvements are evident in patients in the Americas and Europe but not in Asia[266]. A study of all community-dwelling AD patients in Finland diagnosed from 2005 to 2011 with diabetes diagnosed $\geq$ 3 years before AD, in which a total of 7225 cases and 14,528 controls received metformin at least once, found that the adjusted odds of AD were lower among people dispensed metformin for $\geq$10 years[267]. Whether these positive effects occur in the non-diabetic population is not known. Thus far, no studies have investigated the impact of metformin on brain metabolism in human AD patients.

3.1.2. Mitochondrial division inhibitor 1 (Mdivi-1)

One compound, Mdivi-1, which was discovered to be a mitochondrial fission inhibitor through screening a chemical compound library, was later found to be an inhibitor of mitochondrial electron transport chain complex I activity at ~50 μmol/L concentration in multiple types of cells tested[268]. Since Mdivi-1 can pass the blood−brain barrier, 10 and 40 mg/kg of Mdivi-1 was administered by daily oral injection for 1 month in control and APP/PS1 mice and shown to alleviate learning and memory deficits in Morris water maze tests and decrease plaque in APP/PS1 mice[269]. In CRND8 and wildtype mice, i.p. injection of Mdivi-1 at 1.5 mg/30 g once every 2 weeks for 3 months resulted in enhanced learning and memory in the Y-maze test, decreased plaques, increased mitochondrial movement, length, neurite location, and protein content, and increased heme oxygenase-1 protein levels in the hippocampus[270]. The effects of Mdivi-1 administration *in vivo* in animal models on mitochondrial bioenergetics have not been thoroughly investigated.

3.1.3. CP2

The compound CP2 has been found to be a tricyclic pyrone (TP) molecule that attenuated cell death in MC65 cells in response to Aβ oligomers and inhibits Aβ aggregation *in vitro*[271]. CP2 has been shown to be an inhibitor of Acyl-CoA:cholesterol acyltransferase as well as a mild inhibitor of mitochondrial ETC complex I activities (by 20%−45% at 1−50 μmol/L assayed with isolated mitochondria; at 50 μmol/L can reach 80% inhibition with isolated mitochondria)[272−274]. CP2 (2 μmol/L, 24 h) decreased basal, ATP-linked, leak-linked, and non-mitochondrial oxygen consumption rate and stimulated AMPK in cultured primary neurons, decreased ATP, and increased AMP and the AMP:ATP ratio in APP/PS1 brains after 2 months[272,273]. Further related to metabolic regulation, SIRT3, PGC1α, TFAM, GLUT3, and GLUT4 were increased and phospho-PDH:total PDH ratio was decreased 24 h after gavage of CP2 at 25 mg/kg in APP/PS1 mice[274]. Chronic administration (2−14.5 months) improved cognition in the APP/PS1 and 3xTg mouse models of AD and decreased amyloid plaques in APP/PS1 mice after 4 months[272−275].

3.1.4. J147

J147 is a compound derivative from curcumin that exhibits neuroprotective features and low EC_{50}s in multiple cell culture-based assays[276]. It has been shown to improve multiple cognitive tests in rats and the APP/PS1 mouse model of AD, as well as decrease pathology in APP/PS1 mice[276,277]. With a drug-affinity-responsive-target-stability identification approach, it was found that J147 targets ATP5A (a subunit of the mitochondrial complex V). Following its target identification, it has been found that J147 inhibits ATP synthase activity from isolated bovine heart mitochondria, localizes to mitochondria, and increases mitochondrial membrane potential in HT22 cells, as well as elevates total ATP in fly heads[278]. In the SAMP8 premature aging mice, J147 treatment (oral daily administration starting at 3 month of age) preserves a more youthful transcriptional profile in the hippocampus and a more youthful metabolomics profile in the plasma and brain,

comparing three and 10 months of age[278]. It is yet to be shown whether J147 affects mitochondrial bioenergetics in the brain. Nonetheless, because of its bioavailability, penetration of the blood−brain barrier, and apparent lack of toxicity in mice, it is now being used in a phase I randomized, double-blind, placebo-controlled clinical trial with a single ascending oral dose in 64 healthy young and elderly volunteers (NCT03838185).

3.1.5. *S-Equol*

Connected to the previous section discussing sex differences in AD, estrogen or estrogen receptor (ER) agonists have been investigated in AD animal models as well as human patients. One recent study administered *S*-equol (an ERβ agonist produced by intestinal bacteria metabolism of a soy isoflavone component, 10 mg twice a day for 2 weeks) to 15 women with AD. Mitochondrial complex IV activity was measured in protein extracts from the platelets 2 weeks before treatment and 2 weeks after stopping the treatment. Although limited by the number of participating patients, this was the first study that directly measured drug effects on bioenergetics in human AD patients and no doubt will lead to more studies in the future[279]. Furthermore, it is still unclear the extent to which estrogen agonists affect mitochondrial bioenergetics by directly regulating mitochondrial ETC activities or by indirectly regulating mitochondrial quality control; thus, the mechanisms underlying estrogen agonists action remain to be determined.

3.2. *Targeting mitochondrial quality control*

In addition to the regulation of mitochondrial function in cellular metabolism, mitochondria number and metabolic function are regulated by fission and fusion, biogenesis, protease activities, and degradation by the lysosomes. Approaches targeting these processes have been explored in the context of AD therapeutics development.

3.2.1. *Fission*

Above, we discussed Mdivi-1, which inhibits mitochondrial ETC complex I activity and mitochondrial fission, and plays a neuroprotective role in AD animal models. In addition to Mdivi-1, a peptide inhibitor of fission protein DRP1, P110, has been developed based on binding to regions of homology between human DRP1 and FIS1[280]. P110 has been shown to attenuate the decrease of mitochondrial membrane potential in response to neurotoxins in cell models and to attenuate cell death in cell lines and animal models of Parkinson's disease, Huntington's disease, and amyloid lateral sclerosis[280−283]. P110 also enhances mitochondrial bioenergetics in isolated cardiac mitochondria from post-myocardial infarction animals, as well as human iPSC-derived cardiomyocytes expressing toxic proteins[284,285]. Relevant to AD, in N2a cells expressing APPSwe mutant protein, in SH-SY5Y cells exposed to Aβ42, and in human AD patient-derived fibroblasts, P110 attenuates disease model-associated decrease of oxygen consumption rate, citrate synthase activity, levels of selective mitochondrial proteins tested, mitochondrial elongation, and cell death[282]. However, in human skin fibroblasts, both P110 and Mdivi-1 abolished circadian-dependent oscillation of total cellular ATP[286], suggesting that there may be potential detrimental effects of blockade of mitochondrial fission. DA1 is another peptide that was developed based on sequence alignment between DRP1 and its interacting protein, mitochondrial nucleoid protein ATAD3A[287]. There are more ATAD3A pulled down together with DRP1 in Huntington's disease patient iPS cells and HD mouse brains, and DA1 decreases DRP1−ATAD3A interaction and suppresses mitochondrial fragmentation and bioenergetic deficits[287]. Whether DA1 peptide can attenuate neurological and neuropathological defects in AD models has not been tested. Mitochondrial fission can also be enhanced through AMPK activation, resulting in removal of mitochondria[288]. The strategies have not been investigated in preclinical or clinical models of AD.

3.2.2. *hPreP*

Mitochondrial misfolded, oxidized, or damaged proteins can be degraded by some of the mitochondrial proteases, including LONP, ATP-dependent CLP protease, human presequence protease (hPREP), and high temperature requirement A (HTRA)[289]. The observation that transgenic increase of neuronal PREP activity decreased Aβ accumulation, attenuated neuroinflammation and improved cognition in AD mouse models, and increased mitochondrial complex IV activity in cultured hippocampal neurons suggests that hPREP agonists may be neuroprotective in AD[290,291].

3.2.3. *Other mitochondrial-targeted compounds*

A number of mitochondrial-targeted compounds have been tested in preclinical models for attenuating AD-related pathological and neurological deficits. Not all of these have been shown to impact mitochondrial bioenergetics. For example, in a rat model generated based on galactose-rich diet and breeding selection of cataract development with associated accelerated aging in multiple tissues, including declines of cognition (OXYS rat), dietary supplementation with plastoquinonyldecyltriphenylphosphonium (SkQ1) attenuated OXYS-associated decrease of mitochondrial area, density of asymmetric synapses, and neurons in the hippocampus. In addition, SkQ1 decreased Aβ40, Aβ42, total and p-Tau, and improved learning and memory in these rats. Mitochondrial function has not been assessed in SkQ1-treated OXYS rats[292−295]. A ubiquinone compound, MitoQ, which targets the mitochondria due to a covalently bound lipophilic cation triphenylphosphonium, has been shown in 3xTg-AD mice to increase learning and memory and synaptophysin level and decrease GFAP, IBA1, and Aβ42, total and p-TAU[296,297]. A small clinical trial is testing MitoQ effects on carotid artery endothelial function and brain blood flow in mild cognitive impairment patients (ClinicalTrials.gov Identifier: NCT03514875). The mitochondrial-targeted peptide SS-31 associates with cardiolipin in the mitochondrial membrane[298]. In N2a cells exposed to Aβ, mitochondrial numbers are increased, and neuritic outgrowth and cytochrome oxidase activities are decreased, while MitoQ or SS31 both attenuate these Aβ-induced changes. Neuritic outgrowth in primary neurons of Tg2576 mice is also improved by MitoQ or SS31 treatment[299]. In a Tg2576 mouse model, SS31 i.p. injection decreased Aβ levels, increased fusion proteins and synaptic proteins, and increased cytochrome *c* activity[300].

3.2.4. *Metabolites in the mitochondria*

Metabolites from the TCA cycle provide substrates for mitochondrial function as well as signaling and building blocks for other cellular molecules. It has been shown that the levels of the mitochondrial complex II substrate succinate can be modulated by supplementation of malonate and affect ischemia reperfusion injury[301,302]. Itaconate treatment decreased complex II respiration in primary neurons, while its infusion *in vivo* protected against traumatic brain injury[303]. Alpha-ketoglutarate (αkG) has been

shown to extend lifespan in mice[304]. These studies suggest that by changing the relative levels of metabolites important for mitochondrial function, cellular function and survival may be affected.

3.2.5. *Mitophagy*

Aged, dysfunctional, and damaged mitochondria or mitochondrial fragments can be removed *via* mitophagy[305–311]. Many efforts have been made to enhance mitophagy as an approach for disease therapy (Fig. 6)[312]. One key pathway is the targeting of PINK1/Parkin to the mitochondria, PINK1 phosphorylation of Parkin and ubiquitin and Parkin ubiquitination of substrates are involved in the process[305–310]. PINK1/Parkin independent mitophagy also present in various cells and tissues mediated in part by the mitophagy adaptor proteins[305–310]. At present, although compounds that target mitophagy have been identified, some have unknown cellular targets, some have not been shown to impact whole-body or mitochondrial metabolism, and some have not been tested in AD models. In addition, many of the mitophagy adaptors, perhaps including but not limited to NBR1, TAX1BP1, P62, NDP52, FUNDC1, FKBP8, BNIP3, NIX, PGAM5, RHEB, BAX, and BECN, have not been specifically targeted with pharmacological compounds as a mitophagy-enhancement strategy in AD. Some have been targeted using pharmacological agents to enhance or prevent apoptosis or general autophagy, including in AD models. It is conceivable that, in the near future, more compounds targeting these mitophagy adaptors will be developed and tested in potentially different disease models including AD models depending on the mechanisms of action of these adaptor proteins.

As a key protein involved in mitophagy, PINK1 kinase activity has been shown to be enhanced by ATP analogue kinetin triphosphate KTP, kinetin riboside and its ProTides, and mitochondrial uncoupler niclosamide and analogues[313–315]. One strategy that increased PINK1 and Parkin by urolithin A supplementation found enhanced mitophagy without inducing general autophagy, improved oxygen consumption rates that were impaired by Aβ and APOE/E4 in worms and cells, and improved cognition and pathology in the APP/PS1 mouse model, supporting the utility of targeting mitophagy for improvement of bioenergetics in AD[35]. However, the target of urolithin A that mediates the enhancement of mitophagy has not been identified. As a mitochondrial-targeted protein, miro 1 has been shown to be resistant to removal from mitochondria after CCCP in Parkinson's disease fibroblasts but not AD fibroblasts, compared to healthy controls. Using this observation, compound **3** has been identified from a high-throughput screen study and found to decrease Parkinson's disease-related neurodegenerative phenotypes in fibroblasts and fly models. Western blots and immunocytochemistry suggest an impact on mitophagy, although its impact on bioenergetics or AD-related phenotypes is unclear[316].

Large scale screening approaches have identified compounds that enhance mitophagy in both PINK1-Parkin-dependent and independent manners[305–309,312]. Some target proteins that inhibit PINK1-Parkin-dependent mitophagy, including the FT385 and ST-539 compounds that target USP30[317,318] and the BC1464 compound that targets FBXO7[319]. Other studies use reporters or tags as a drug discovery strategy to identify mitophagy-enhancement compounds, including using mitochondria-targeting AUTAC (autophagy-targeting chimera) to identify AUTAC4 that target TSPO[320]. Using mitoQC, iron chelators including deferoxamine have been shown to stimulate mitophagy independent of PINK1 and Parkin in SH-SY5Y cells, and time dependently decreased mitochondrial respiration without increasing DCFDA fluorescence as a measure of reactive oxygen species[321]. It is unclear whether these compounds are protective against AD-related phenotypes. It has also been shown that LRRK2 kinase inhibitor GSK3357679 rescued mitophagy defects in LRRK2 G2019S mice[322]. It has been reported that LRRK2 kinase inhibitors LRRK2-IN-1 or PF-06447475 rescue RAB10 accumulation on depolarized mitochondria in LRRK2 mutant fibroblasts, which may be the mechanism allowing RAB1−OPTN interaction and rescue mitophagy

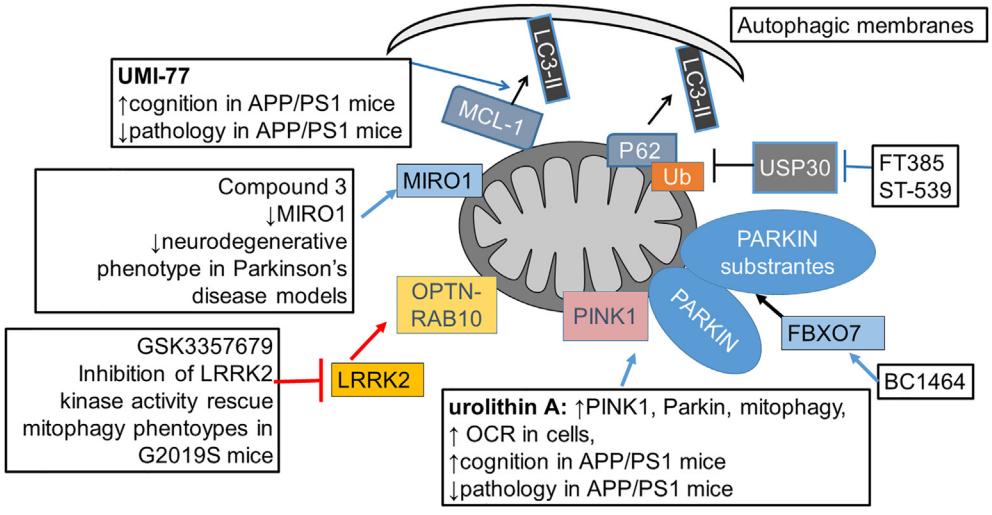

Figure 6 Examples of compounds that enhances mitophagy. Urolithin A and UMI-77 have been shown to improve cognition and decrease pathology in the APP/PS1 model of AD. Urolithin A increases mitophagy by increasing PINK1 and Parkin and improves bioenergetics in cells and worms. UMI-77 enhances MCL-1 and LC3 interaction on mitochondria, and show benefits in attenuating cognitive deficits and pathology in APP/PS1 mice. The impact of other mitophagy enhancement compounds on AD phenotypes is unclear. Compound **3** enables MIRO1 removal and decreases Parkinson's disease-related phenotypes. LRRK2 kinase inhibitors potentially decrease RAB10 phosphorylation, enable OPTN−RAB10 interaction on mitochondria, and restore mitophagy defects caused by LRRK2 mutation. FT385, ST-539, and BC1464 target Parkin-related mitophagy mechanisms, and while their targets are known, their effects on bioenergetics or AD phenotypes are unclear.

and mitochondrial function[323]. Whether enhancement of mitophagy through inhibition of LRRK2 kinase activity is beneficial for metabolism and bioenergetics and for alleviating AD phenotypes is still unclear.

Using mito-SRAI, which localize to mitochondria, as a mitophagy reporter, chemical inducers of mitophagy have been identified, including those that spare mitochondrial respiration in a Seahorse XF stress test assay, although the molecular targets of the inducers are currently unclear[324]. Using mt-Keima as a reporter protein, a pharmacological compound UMI-77 has been identified, which induces mitophagy in an ATG5 dependent, NBR1, TAX1BP1, P62, NDP52, FUNDC1, BNIP3, NIX, BAX, BECN, and PARKIN independent manner, by targeting MCL-1 that bind to LC3A on mitochondria[325]. In the APP/PS1 mouse model of AD, UMI-77 mitigates cognitive deficits and pathology[325]. Whether mitochondrial function is improved by UMI-77 is unclear.

3.3. *Neuroinflammation and DAMPs*

Neuroinflammation is a common theme among neurodegenerative disorders, including AD. Similarly, mitochondrial dysfunction and oxidative stress have been associated with pathologies of these diseases. High levels of pro-inflammatory mediators can be found in the brain and CSF of mild cognitive impairment (MCI) and AD patients[326–332]. In this respect, damage-associated molecular patterns (DAMPs) have been found in AD and other diseases[326,333]. DAMPs are intra- and extra-cellular molecules released during periods of cellular stress that activate innate immune response *via* interactions with specific receptors and signaling pathways. Whereas DAMPs can be released from multiple cellular compartments and organelles following stress, mitochondria can release various molecules that intra- and extracellularly initiate innate immune response. It is perhaps not surprising, therefore, that mitochondrial dysfunction and mtDNA alterations have been noted in AD[334–347].

Mitochondria are ancient α-proteobacterial symbionts; hence, they have many bacterial-like constituents, including *N*-formyl peptides, cardiolipin, and DNA (exhibiting low methylation at CpG sites), that when released from the organelle act as mitochondrial DAMPs (mtDAMPs; Fig. 7)[348–350]. *N*-Formyl peptides stimulate the secretion of cytokines by activating the formyl peptide receptor 1 (FPR-1) receptor[351]. Mitochondrial reactive oxygen species (ROS) production can activate mitochondrial antiviral signaling (MAVS) proteins on the outer mitochondrial membrane (MAVS are also activated by proteins that detect viral RNA) that can induce immune and inflammatory gene expression through the regulation of NF-κB and interferon regulatory factor[352–354], independent of cytosolic viral sensors[350]. MAVS also promote the activation of the nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing protein (NLR)-like receptor family pyrin domain containing 3 (collectively referred to as NLRP3) inflammasome, while cardiolipin recruits NLRP3 to the outer membrane during mitochondrial membrane depolarization when it translocates from the inner to the outer membrane[355]. Fragments of the mitochondrial DNA (mtDNA) interact with TLR9 (toll-like receptor 9), activating the NF-κB signaling pathway and transcription of proinflammatory cytokines such as TNFα and IL-6[351,356,357]. Both mtDNA DAMPs and mitochondrial-generated ROS can activate the NLRP3 inflammasome, triggering inflammation (production of IL-1β and IL-18) and cell death[358–360]. Finally, in the cytosol, mtDNA can induce conformational changes in cyclic GMP/AMP synthase (cGAS) that facilitate interactions with stimulator of interferon genes (STING) that activate interferon regulatory factor 3 (IRF-3), which triggers the expression of interferon-stimulated genes and potentiates interferon responses[361].

MtDNA copy number decreases and increased heteroplasmy have been noted in neurons from postmortem brains of AD patients[362,363], and it has been noted that mitochondrial proteins and mtDNA sustain oxidative damage early in AD, suggesting mitochondrial dysfunction as an early phase in disease progression[364,365]. Interestingly, amyloid β (Aβ) peptide and neurofibrillary tangles have been implicated in mitochondrial dysfunction, as these proteins have been known to impact mitochondrial import machinery and to detrimentally affect organelle

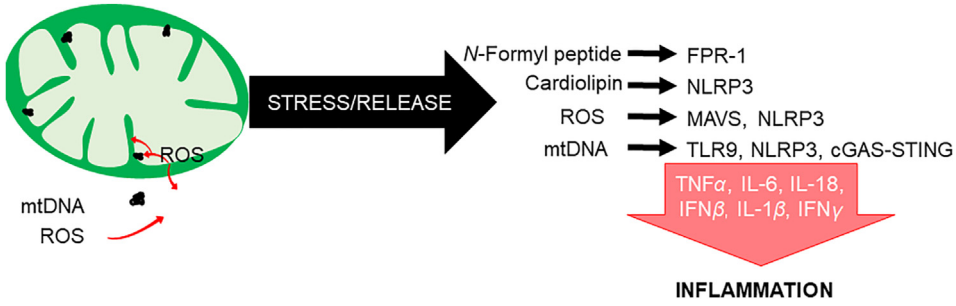

Figure 7 Mitochondrial-mediated immune functions and cell signaling. Under conditions of stress, mitochondria can release molecules such as *N*-formyl peptides, ROS, mtDNA, and cardiolipin. These components can initiate an immune response and related signaling pathways in the cytosol or extracellular space. *N*-Formyl peptides are released and act as chemoattractants for neutrophils, binding to the formyl peptide receptor 1 (FPR-1) and promoting their activation and release of pro-inflammatory cytokines including TNFα, IL-1β, and IFNγ. Cardiolipin translocates from the inner to the outer mitochondrial membrane, where it interacts with the nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing protein (NLR)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. ROS activates mitochondrial anti-viral signaling (MAVS) protein located on the outer membrane, triggering activation of the NF-κB pathway and the release of interferon-regulating factors (IRFs). Additionally, MAVS can promote the oligomerization and activation of the NLRP3 inflammasome. MtDNA fragments (or components containing mtDNA, *e.g.*, mtDNA nucleoids) released from the organelle bind TLR9 receptors that activate NF-κB signaling or, in the cytosol, initiate cyclic GMP/AMP synthase—stimulator of interferon genes (cGAS–STING) pathways that potentiate interferon responses. Individually or collectively, these mitochondrial-initiated processes mediate a cascade of pro-inflammatory pathways and cytokines that contribute to innate immune response.

bioenergetics and increase ROS production[366–368]. The combination of increased oxidant response and declining ATP production not only increases the possibility of mitochondrial-mediated apoptosis, but also the risk of mtDAMP release[349]. Injection of mitochondrial lysates or mtDNA into mouse hippocampus has also been shown to have pro-inflammatory effects consistent with the alteration of AD-related pathways[369]. It is also noteworthy that fragments of APOE4, the E4 variant of apolipoprotein E (which is a major susceptibility gene for sporadic AD) is associated with mitochondrial dysfunction and oxidative stress when localized to the mitochondrion in hippocampal neurons[370,371]. Finally, observations that mtDAMPs are components of circulating extracellular vesicles with aging and neurodegeneration[372,373] are consistent with a mito-centric role/etiology in AD development.

Because innate immunity appears to play a role in many forms of neurodegenerative diseases including AD, studies examining how mtDAMP release influences disease development are of interest. It is likely that release of such molecules initially is protective temporally; for example, it has been noted that TLR9 activation can lead to behavioral improvements in transgenic AD mice and decreased extracellular Aβ and associated Tau pathology, suggesting that TLR9 stimulation may be beneficial for microglial function in mouse models of AD[374,375]. However, chronic induction of these pathways results in inflammatory processes that contribute to neurodegeneration. Hence, therapies targeting mtDAMPs and/or their downstream pathways may be efficacious in treating AD. For example, while defects in mitophagy can contribute to organelle dysfunction, it also contributes to the release of mtDAMPs as part of the quality-control process—in this respect, the finding that pharmacologic restoration of mitophagy improves cognitive deficits and decreases Aβ accumulation in mouse models supports this notion[376]. Similarly, reduced tau phosphorylation and microglia-induced inflammation have been observed subsequent to pro-mitophagic pharmacological treatments[35].

4. Conclusions and future directions

Metabolic perturbations, both at the systemic level and at the intracellular mitochondria, are linked to both aging and AD. Based on that diabetes may be a risk factor for AD, and that abnormal glucose metabolism and insulin signaling occur in AD brains, targeting whole-body and brain insulin pathways has been considered as an intervention strategy for AD. Recent studies have also highlighted the contributions of sex, gut microbiome, and circadian regulation in both whole-body and mitochondrial-mediated metabolism, which present additional potential targets for development of AD therapeutics. Compounds that affect mitochondrial bioenergetics and mitochondrial quality control, as well as mitochondria-linked inflammatory responses, have been tested and refined in current preclinical models and considered for clinical trials.

Based on our current understanding of metabolism and mitochondrial bioenergetics, major barriers to developing AD therapy with metabolism and bioenergetics as targeted pathways are as follows: 1) Few preclinical studies have measured parameters of mitochondrial bioenergetics in the blood or the brain after therapeutic interventions targeted at metabolism in AD. 2) A coordinated effort in assessing the extent and aspects of corresponding whole-body metabolism versus mitochondrial bioenergetics in blood or brain samples is needed in the context of AD. 3) Although there is more awareness of gut microbiome, sex, and circadian time as biological variables, scarcely any studies test mitochondrial bioenergetics with these in mind. 4) There are still limited system biology studies linking whole-body and mitochondrial energetics to transcripts, proteins, and post-translationally modified proteins.

These major barriers can be overcome with recent development of new method that enables measurement of mitochondrial bioenergetics in cells, blood and tissues[377,378], with integrated views of whole-body metabolism and mitochondria-mediated metabolism, with consideration of gut–brain axis, sex and circadian regulation, and with system biology-omics analyses of connectomes and networks[379–383]. Over the next 10 years, we will witness more studies in these exciting areas that will impact how we view AD therapy. Major breakthroughs may involve a better understanding of the interconnection of whole-body and brain metabolism.

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Author contributions

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Conflicts of interest

We have no competing interests to declare.

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