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Chapter 4

Mitochondrial Link Between Metabolic Syndrome and Pre-Alzheimer's Disease

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Abstract

There is much evidence to demonstrate that the presence of the metabolic syndrome (MetS) is associated with an increase in the incidence of pre-Alzheimer's disease. The possible underlying mechanisms linking pre-Alzheimer's disease and MetS are still unclear. This study summarizes and discusses the potential mechanisms involved in pre-Alzheimer's disease under MetS conditions, including an increased brain oxidative stress, brain inflammation, brain mitochondrial dysfunction, hyper-phosphorylated tau protein, and amyloid beta production. This report focuses on brain mitochondrial alterations in cases of pre-Alzheimer's disease where MetS is also extant. The data from *in vitro*, *in vivo*, and clinical studies are included. In addition, potential interventions against pre-Alzheimer's disease in conjunction with MetS are summarized and discussed.

Keywords: mitochondria, brain, cognitive impairment, obesity, oxidative stress, inflammation

1. Introduction

1.1. Metabolic syndrome, pre-Alzheimer's disease, and brain mitochondria

According to the consensus statement of the International Diabetes Federation, metabolic syndrome (MetS) is defined as abdominal obesity plus any two of four factors including raised triglycerides, reduced high-density lipoprotein (HDL) cholesterol, raised blood pressure, and elevated fasting plasma glucose [1]. The risk factors of MetS include genetic factors, physical inactivity, and too high a calorie intake or poor diet [2, 3]. It has been postulated that insulin

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resistance is the main contributor toward MetS. Insulin resistance is a pathological condition, in which target tissues cannot take up glucose into the cells at the physiological insulin level. It is characterized by hyperinsulinemia with euglycemia. MetS is often represented by an obese-insulin-resistant condition. It can lead to the development of not only cardiovascular diseases but also stroke [4] and neurodegeneration [5]. In addition, data from clinical trials have indicated that hyperinsulinemia during insulin resistance is related to cognitive decline in elderly adults [6, 7]. MetS has been induced in several animal models to enable the investigation of the mechanisms responsible for the adverse effects of the MetS condition on cognitive impairment. MetS has been induced in animal models by using high-fat/high-calorie diet consumption. Interestingly, previous studies have investigated the effects of long-term high-fat diet (HFD) consumption on metabolic and brain dysfunction [8, 9]. Those data demonstrated that the consumption of a HFD for 8 weeks caused obese-insulin resistance or MetS, as indicated by central obesity, hyperinsulinemia, dyslipidemia, and raised blood pressure [8, 9]; however, cognitive impairment and brain insulin resistance were observed later at the end of 12 weeks of HFD consumption [8, 10]. Those findings suggest that the metabolic disturbance preceded cognitive dysfunction in induced MetS

Pre-Alzheimer's disease or mild cognitive impairment (MCI) is a condition of memory decline but does not significantly affect the normal function of a person's life [11]; however, Alzheimer's disease (AD) is an irreversible chronic neurodegenerative disease and it is the most common type of dementia [12]. The presence of neurofibrillary tangles and amyloid beta deposition in the brain is hallmarks of AD [12]. Recent studies have shown that the incidence of AD has increased in MetS subjects [13–15]. Those findings suggest that there is a possible connection in the pathogenesis between MetS and AD. Data from a clinical study suggest that oxidative stress is a key component that regulates the development of AD in MetS subjects [15]

Mitochondria are known as the major source of oxidative stress [16]. Brain mitochondrial dysfunction was observed in several pathological conditions, including MetS and AD [17–22]. That dysfunction causes increased oxidative stress [10] and leads to the activation of several stress kinases [19]. Subsequently, a raised oxidative stress impaired brain insulin receptor function [23], inhibited insulin-degrading enzymes and increased beta-secretase activity [23, 24], resulting in increased hyperphosphorylated tau and amyloid beta deposition in the brain [19]. Therefore, brain mitochondrial dysfunction could be an important feature in AD pathogenesis in the MetS condition. Furthermore, the elevation of oxidative stress caused the imbalance of brain mitochondrial dynamics [25]. Mitochondrial dynamics are a key process for the maintenance of cell life and death through the balancing of mitochondrial fission and fusion [26]. In the physiological status of the brain, mitochondrial dynamics enables mitochondria to recruit subcellular components, exchange substrates between mitochondria, and control mitochondrial shape [26]. Recently, it has been proposed that brain mitochondrial dynamic imbalance is another mechanism that is involved in the brain pathogenesis of MetS and AD [27, 28]. Examples from the recent research are as follows: (1) several studies have reported that levels of Dynamin-related protein 1 (Drp1) and mitochondrial fission 1 (Fis1), markers of mitochondrial fission, were increased in the brains of MetS and AD animals [29, 30], leading to neuronal apoptosis [29]; (2) mitochondrial fusion protein levels were decreased in the brains of both MetS and AD animals [29, 30]. Therefore, a mitochondrial dynamic imbalance may play an important role in cognitive dysfunction in MetS and AD [26, 30]

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2. The implications of metabolic syndrome on brain mitochondria and its association with the development of AD: *in vivo* studies and clinical studies

2.1. MetS condition from a high-fat diet-induced obese-insulin-resistant model

Obese-insulin resistance is characterized by body weight gain and peripheral insulin insensitivity [20–22, 31–34]. These characteristics are similar to those seen in the MetS condition in humans. In addition to peripheral insulin resistance, brain insulin resistance has also been reported in the obese condition in rats [20–22, 31, 34]. A diet containing 60% E from fat is considered to be a high-fat diet (HFD), and it has been widely used to induce obese-insulin resistance in rodents [20–22, 31–33]. In some studies, it has been found that HFD consumption increased plasma cholesterol and free fatty acid levels [20–22, 31, 32, 34]. However, the plasma glucose level was not increased, but hyperinsulinemia was observed following HFD consumption even after long-term consumption of a HFD (12 months), indicating a pre-diabetic state [20, 31–34].

HFD consumption between 16 weeks and 12 months caused brain mitochondrial damage, including an increased mitochondrial ROS production [20–22, 31, 34], a reduced mitochondrial membrane potential [19, 31, 34–36], and an impaired mitochondrial morphology as indicated by an increased mitochondrial swelling [20–22, 31, 33]. Furthermore, HFD reduced adenosine triphosphate (ATP) production [34]. Although several studies suggested that HFD caused brain mitochondrial dysfunction, Jorgensen et al. reported that HFD did not impair brain mitochondrial function even when the rats were given a HFD for 12 months. Therefore, the effects of a HFD on brain mitochondrial function still need to be elucidated.

There are several studies which have shown that brain mitochondrial damage could impair cognitive function and synaptic plasticity [20–22, 31, 33, 34]. Various cognitive tests have been used such as the Morris water maze (MWM), novel object recognition (NOR), novel object smelling (NOS), and Y-maze test. The MWM and Y-maze are tests for hippocampal-dependent learning process, including the acquisition of spatial memory and long-term spatial memory [36]. NOR and NOS are used to assess non-force driving and spontaneous memory [35, 37].

Rats and mice fed on a HFD for 16–20 weeks had an increased time to reach the platform and a decreased time in the target quadrant and crossing target number, compared with normal diet (ND)-fed animals, when cognitive function was assessed using the MWM [20–22, 31, 34]. Furthermore, recognition index was decreased in HFD-fed mice, compared to ND-fed mice [34]. Mice fed on a HFD for 12 months did not indicate an impaired discrimination index following the NOS test, but there were decreased percentage correction alterations in the Y-maze test [33]. These accumulative data suggested that the consumption of a HFD caused obese-insulin resistance, brain mitochondrial dysfunction, and synaptic dysplasticity, possibly leading to cognitive dysfunction. However, no study has demonstrated brain mitochondrial dysfunction with elevated AD markers such as Aβ levels and hyperphosphorylated tau in HFD-fed animals. This suggests that obese-insulin resistance can lead to the development of brain mitochondrial dysfunction and cognitive impairment or MCI or pre-AD without AD symptoms. Data regarding the effects of HFD-induced obese-insulin resistance on brain mitochondria and its association with the development of AD are shown in **Table 1** and are summarized in **Figure 1**.

Study model	Major findings					Refs
Animal/diet/duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
Wistar rats/HFD (60% E fat) or ND (20% E fat)/16 weeks	• ↑ BW, insulin, HOMA, cholesterol • ↔Glucose • ↓Peripheral insulin sensitivity • ↓Brain insulin signaling	• ↑ ROS • ↓ MMP ○ ↑Swelling	*MWM* • ↑Time to reach platform • ↓Time in target quadrant *Synaptic plasticity* • ↓LTP	N/A	HFD-induced obese-insulin resistance leads to synaptic dysplasticity and brain mitochondrial dysfunction and finally results in cognitive decline.	[20–22, 31]
C57BL/6 mice/HFD or ND/20 weeks	• ↑BW, insulin, HOMA, FA, cholesterol • ↓Peripheral insulin sensitivity • ↓Brain insulin signaling	• ↑ROS • ↓MMP • ↓ATP	*NOR* • ↓Recognition index *MWM* • ↓Time in target quadrant • ↓Crossing target number	N/A	HFD-induced obese-insulin resistance leads to brain mitochondrial dysfunction and cognitive dysfunction.	[34]
C57BL/6 mice/HFD (60% E fat) or ND (12% E fat)/12 months	• ↑ BW, insulin • ↔Glucose	• ↑Swelling (elongated mitochondria)	*NOS* • ↔Discrimination index *Y-maze test* • ↓% Correct alterations *Synaptic plasticity* • ↓Synaptic density	N/A	HFD-induced obese-insulin resistance leads to synaptic dysplasticity, brain mitochondrial dysfunction and cognitive dysfunction.	[47]
Wistar rats/HFD (60% E fat) or ND (13% E fat)/12 months	• ↑BW, insulin, HOMA, FA • ↔Glucose	• ↔ State 3, 4 respiration • ↔ RCR	N/A	N/A	HFD-induced obese-insulin resistance does not impair brain mitochondrial function.	[32]

Abbreviations: BW, body weight; HOMA, homeostasis model assessment; HFD, high-fat diet; ND, normal diet; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; RCR, respiratory control ratio; MWM, Morris water maze; LTP, long-term potentiation; NOR, novel object recognition; NOS, novel smell recognition; N/A, not assessed.

Table 1. Implications of obese-insulin resistance on brain mitochondria and its association with the development of Alzheimer's disease.

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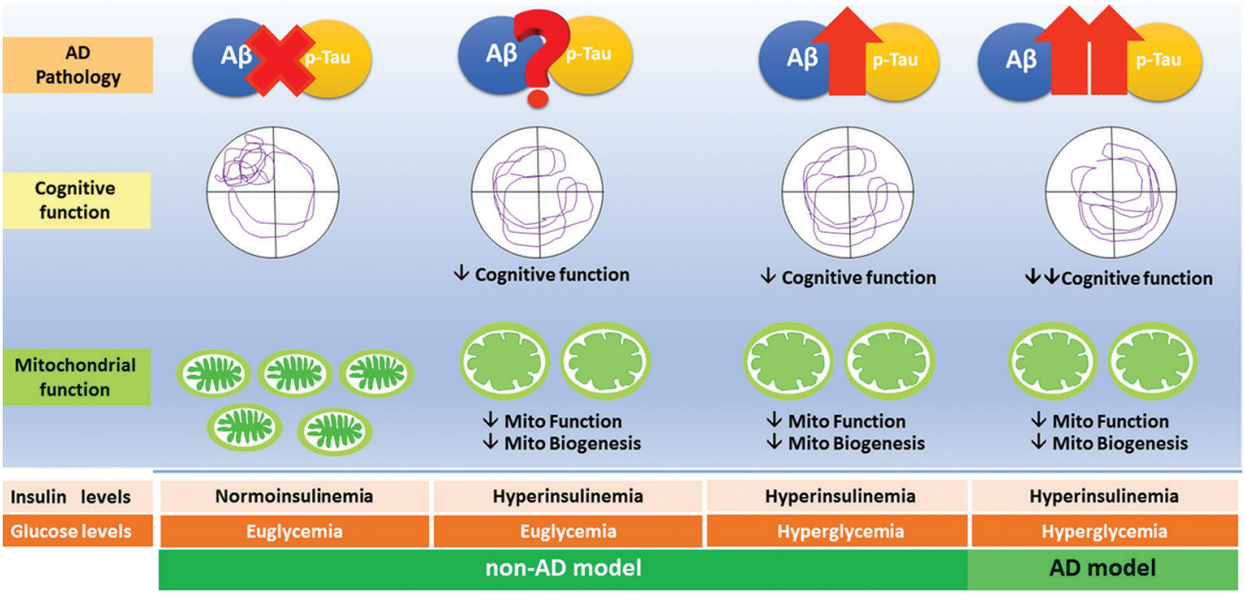


Figure 1. The effects of insulin resistance and T2DM on brain mitochondria and their association with the development of Alzheimer's disease in non-AD and AD models.

2.2. Type 2 diabetes mellitus model

Type 2 diabetes mellitus (T2DM) is diagnosed when hyperglycemia is observed along with insulin resistance [38–41]. In order to create a T2DM animal model, a combination of a HFD with low-dose streptozotocin, and a high-calorie diet were used [38–41]. Both regimens caused hyperglycemia in rodents [38–41]. Similar to obese-insulin-resistant models, T2DM animals are also found to develop brain mitochondrial damage [38–41].

Beside the effects of T2DM on oxidative stress and mitochondrial membrane depolarization, nuclear respiratory factor 2 (NRF2) levels were reduced in the brains of T2DM mice [38]. NRF2 acts as an antioxidant and detoxifying enzyme and helps to reduce oxidative stress in mitochondria [42]. Therefore, a decreased level of NRF2 directly impairs the brain mitochondrial redox system, which leads to the reduction of brain mitochondrial antioxidant capacity. In addition, a previous study showed a decrease in brain mitochondrial numbers in T2DM mice [41]. The possible explanation may be due to a decrease in NRF2 in the brain of T2DM mice, in which NRF2 regulates brain mitochondrial biogenesis [43]. These data indicate that T2DM caused brain mitochondrial damage and brain mitochondrial dysfunction, resulting in an increased brain oxidative stress.

Consistent with the findings from obese-insulin-resistant animals, T2DM animals also developed brain mitochondrial dysfunction with cognitive impairment, quantified using the MWM test, as indicated by an increased escape latency and time in target quadrant and a decreased crossing target number [39, 41]. Also, T2DM rats had decreased percentage correction alterations and total distance, when the abilities of these animals were investigated using the Y-maze test [39]. T2DM also affected brain synaptic plasticity proteins, as indicated by reducing postsynaptic density protein 95 (PSD95) and synaptosomal-associated protein 25 (SNAP25) levels [38]. However, T2DM did not affect synaptophysin protein levels [38].

In the T2DM model, brain mitochondrial markers were evaluated along with the changes in AD markers. It is interesting that T2DM rats developed AD signs, specifically that the levels of AD markers, including Aβ42 and hyperphosphorylated tau, were significantly increased in T2DM rats, when compared with non-T2DM rats [39, 41]. In addition, acetylcholine esterase enzyme activity was increased, and ACh levels were decreased in the brains of T2DM mice [39]. These data suggested that T2DM rats had impaired brain mitochondrial dysfunction and synaptic plasticity, leading to cognitive dysfunction and showed increased AD markers. Interestingly, those findings indicated that AD was developing in the T2DM condition. Contrary to the findings from animal studies, when Loo et al. investigated the effect of T2DM on mitochondrial function in human mononuclear cells, their data showed that T2DM did

Study model	**Major findings**					**Refs**
Animal/diet/ duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
SD rats/HFD (60% E fat) + STZ (30 mg/kg, i.p.) or ND + citrate buffer/11 weeks	• ↑BW, insulin, glucose • ↓Peripheral insulin sensitivity • ↓Brain insulin signaling	• ↓Mito number • ↑ROS • ↓MMP	*MWM* • ↑Escape latency • ↓Crossing target number	• ↑Aβ42	T2DM causes brain mitochondrial dysfunction, increases levels of AD markers, and cognitive dysfunction.	[41]
C57BL/6 mice/ HFD (60% E fat) or ND (10% E fat)/10 weeks	• ↑Glucose	• ↑ROS • ↓MMP • ↓ATP	*MWM* • ↑Escape latency • ↓Time in target quadrant *Y-maze test* • ↓% Correct alterations • ↓Total distance	• ↑pTau/ Tau • ↑AChE activity • ↓ACh	T2DM causes brain mitochondrial dysfunction, increases levels of AD marker, and cognitive dysfunction.	[39]
Wild-type mice/ sucrose(20%) solution or control (water)/7 months	• ↑BW, insulin, HbA1c	• ↓RCR • ↓MMP • ↓ATP • ↓NRF2	*Synaptic plasticity* • ↓PSD95 *SNAP25* • ↔Synaptophysin	N/A	T2DM causes mitochondrial dysfunction and impairs synaptic plasticity.	[38]
T2DM patients compared to healthy controls	N/A	• ↔ROS • ↔MMP • ↔ATP	N/A	N/A	T2DM is not associated with mitochondrial dysfunction.	[40]

Abbreviations: BW, body weight; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; HFD, high-fat diet; ND, normal diet; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; Ach, acetylcholine; AChE, acetylcholine esterase; ATP, adenosine triphosphate; RCR, respiratory control ratio; NRF, nuclear respiratory factor; MWM, Morris water maze; N/A, not assessed.

Table 2. Implications of type 2 diabetes mellitus (T2DM) on brain mitochondria and its association with the development of Alzheimer's disease.

not affect mitochondrial function [40]. Their findings showed that T2DM affected regional mitochondria, but not systemic mitochondria. Data regarding the effects of T2DM on brain mitochondria and its association with the development of AD are shown in **Table 2** and are summarized in **Figure 1**.

3. The implications of high-calorie diet consumption on brain mitochondrial function and brain function in an AD model: *in vivo* studies

Two AD animal models, including 3xTg AD mice and APPswe/PS1dE9 mice, have been used to investigate the implications of high-calorie diet consumption on brain mitochondrial function

Study model	**Major findings**					**Refs**
Animal/diet/ duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
3xTgAD mice/HFD (60% E fat) or ND (12% E fat)/12 months	- ↑ BW - ↔ Glucose, insulin	• ↔Mito number • ↔Mito morphology	*NOR* • ↔Discrimination index *Y-maze test* • ↔ % Correct alterations *Synaptic plasticity* • ↔ Synaptic number	• ↔Aβ42	Obesity did not alter brain mitochondria and AD markers AD model.	[33]
APPswe/PS1 dE9 mice/HFD (45% E fat) or ND/12 weeks	• ↑BW • ↔Brain insulin signaling	• ↓PGC1α • ↔NRF1,2 • TFAM	N/A	• ↑APP • ↓ADAM10 • ↓IDE • ↔BACE1 • ↑Cortical soluble Aβ40, Aβ42 insoluble Aβ42	Obesity increased AD markers, but did not alter brain mitochondrial biogenesis in AD model.	[17]
APPswe/PS1 dE9 mice/HFD (45% E fat) or ND/24 weeks	• ↑BW, insulin, glucose • ↓Peripheral insulin sensitivity • ↓Brain insulin signaling	• ↓PGC-1α • ↓NRF1,2	*NOR* • ↓Discrimination index	• ↔APP p-Tau/Tau • ↓IDE • ↑Cortical insoluble Aβ42	Obesity increased AD markers, impaired brain mitochondria biogenesis, and cognitive function in AD model.	[18]

Study model	Major findings					Refs
Animal/diet/ duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
Sucrose (20% sucrose) fed mice or 3xTgAD mice fed with ND	N/A	• ↔RCR • ↔MMP • ↔ATP • ↔NRF2	*Synaptic plasticity* • ↔PSD95, synaptophysin, SNAP25	N/A	T2DM and AD mice exhibited similar phenotypes as regards brain synaptic plasticity and brain mitochondrial function.	[38]

Abbreviations: AD, Alzheimer's disease; HFD, high-fat diet; ND, normal diet; BW, body weight; PGC, peroxisome proliferator-activated receptor gamma; NRF, nuclear respiratory factor; TFAM, mitochondrial transcription factor A; RCR, respiratory control ratio; MMP, mitochondrial membrane potential; ATP, adenosine triphosphate; PSD, postsynaptic density protein; SNAP, synaptosomal-associated protein; NOR, novel object recognition; N/A, not assessed.

Table 3. Implications of high-calorie diet consumption on brain mitochondria and brain function in an Alzheimer's disease model.

and brain function. 3xTg AD mice cells with the mutations Thy-1.2-driven APP-Swedish and tau P301L were co-injected into a homozygous PS1M146V knock-in background. This type of AD mice had parenchymal plaque by 6 months of age combined with tau pathology by 12 months of age [44]. In APPswe/PS1dE9 mice, APP/PS1 animals co-express a Swedish (K594 M/N595 L) mutation of a chimeric mouse/human APP (Mo/HuAPP695swe), together with the human exon-9-deleted variant of PS1 (PS1-dE9), which leads to an increase in human Aβ peptide secretion in the brain of APPswe/PS1dE9 mice [17, 18].

There is only one study that has compared the brain mitochondrial function between T2DM and AD animal models. The investigators reported that both T2DM and AD mice had similar degrees of brain mitochondrial dysfunction, decreased synaptic plasticity proteins levels, and raised AD markers [38]. Those findings indicated that AD pathology was developed in T2DM animals, with an involvement of brain mitochondrial dysfunction.

The provision of a HFD to AD mice resulted in a different outcome depending on a genetic background of the AD mice. In 3xTg AD mice, the provision of a HFD led to increased body weight, but did not alter plasma glucose and insulin levels, compared to 3xTg AD mice given an ND [33]. In addition, the brain mitochondrial number and brain mitochondrial morphology, as well as cognitive function and AD markers were not affected by the HFD [33]. The data from this study suggested that T2DM did not alter brain mitochondria, cognitive function, or AD markers in 3xTgAD mice. By contrast, the consumption of a HFD led to a markedly decreased brain mitochondrial biogenesis and aggravated cognitive impairment in APPswe/PS1dE9 mice [17, 18]. Furthermore, a HFD aggravated AD pathogenesis in APPswe/PS1dE9 mice, as indicated by increased cortical soluble and insoluble Aβ, and decreased insulin-degrading enzymes [17, 18]. Data regarding the effects of consumption of a high-calorie diet on brain mitochondrial function and brain function in the AD model are shown in **Table 3** and are summarized in **Figure 1**.

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4. Therapeutic approaches on rats with the MetS condition specific to brain mitochondrial dysfunction and its association with the development of AD

Several studies have used various interventions on brain mitochondria and described their associations with the development of pre-AD. In this report, we have separated these interventions into three categories: (1) antidiabetic drugs, (2) traditional medicine, and (3) other drugs.

4.1. Antidiabetic drugs

Several studies have demonstrated the beneficial effects of antidiabetic drugs on insulin sensitivity and brain mitochondrial function [21, 31, 45]. Our previous study found that the sodium glucose cotransporter 2 (SGLT2) inhibitor, which is a new antidiabetic drug, could decrease metabolic disturbance, brain mitochondrial ROS production, brain mitochondrial membrane potential change, brain mitochondrial swelling, synaptic dysplasticity and cognitive decline in HFD-fed rats [21]. In addition, the incretin-based drugs such as sitagliptin and vildagliptin, dipeptidyl peptidase-4 (DPP-4) inhibitors, also had beneficial effects on the improvement of insulin sensitivity, brain mitochondrial function and cognitive function in HFD-fed rats [21, 31, 45]. Another incretin-based drug, liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, also improved insulin sensitivity and decreased brain mitochondrial swelling [45]. All of these findings indicated that the antidiabetic drugs could reduce peripheral and brain insulin resistance, leading to improvement in cognitive function and synaptic plasticity and were associated with improved brain mitochondrial function. However, there is still lack of evidence showing the effects of antidiabetic drugs on AD markers. Data pertinent to the effect of antidiabetic drugs on brain mitochondrial dysfunction and their association with the development of pre-AD in the MetS condition are shown in **Table 4**.

4.2. Traditional medicine

Several studies have shown the beneficial effects of traditional medicine on brain mitochondrial function in HFD-fed, T2DM and AD rat models [20, 34, 39, 41]. Naringin, a citrus flavonoid, can improve insulin sensitivity and decrease brain mitochondrial ROS production, brain mitochondrial membrane potential change, brain mitochondrial ATP production, and cognitive decline in HFD-fed mice [34]. Furthermore, our previous studies found that garlic extract reduced peripheral and brain insulin resistance, brain mitochondrial ROS production, brain mitochondrial membrane potential change, and brain mitochondrial swelling, leading to improved cognitive function in HFD-fed rats [20]. The ZiBuPiYin recipe (ZBPYR), a traditional Chinese medicine, reduced brain mitochondrial ROS production, increased brain mitochondrial membrane potential change, increased brain mitochondrial number, and decreased cortical insoluble Aβ42, leading to improved cognitive function in T2DM mice [41]. *Dendropanax morbifera* (Araliaceae), a herbal medicine in Asia, improved peripheral and brain insulin sensitivity, decreased brain mitochondrial ROS

Study model	Major findings					Refs
Animal/ interventions/ duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
HFD-fed rats/ SGLT2 inhibitor (1 mg/kg) or vehicle/4 weeks	• ↓BW • ↑Peripheral insulin sensitivity • ↑Brain insulin signaling	• ↓ROS • ↑MMP • ↓Swelling	*MWM* • ↓Time to reach platform • ↑Time in target quadrant *Synaptic plasticity* • ↑LTP	N/A	SGLT2 inhibitor reduced peripheral and brain insulin resistance, improved brain mitochondrial function, and improved cognitive function and synaptic plasticity in obese-insulin-resistant rats.	[21]
HFD-fed rats/ vildagliptin (3 mg/kg) or vehicle/3 weeks	• ↔ BW • ↓Insulin HOMA	• ↓ROS • ↑MMP • ↓Swelling	*MWM* • ↓Time to reach platform • ↑Time in target quadrant	N/A	DPP-4 inhibitor reduced peripheral and brain insulin resistance, improved brain mitochondrial function, and improved cognitive function in obese-insulin-resistant rats.	[31]
HFD-fed rats/ sitagliptin (30 mg/kg) or vehicle/3–4 weeks	• ↔ BW • ↓Insulin HOMA	• ↓ROS • ↑MMP • ↓Swelling	*MWM* - ↓ Time to reach platform - ↑ Time in target quadrant	N/A	DPP-4 inhibitor reduced peripheral and brain insulin resistance, improved brain mitochondrial function, and improved cognitive function in obese-insulin-resistant rats.	[31, 45]
HFD-fed rats/ liraglutide (0.6 mg/kg) or vehicle/3 weeks	• ↔ BW • ↓Peripheral insulin sensitivity	• ↓Swelling	N/A	N/A	Liraglutide reduced peripheral resistance and improved brain mitochondrial function in obese-insulin-resistant rats.	[45]

Abbreviations: HFD, high-fat diet; ND, normal diet; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium glucose transporter 2; BW, body weight; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; MWM, Morris water maze; NA, not assessed.

Table 4. Potential effects of antidiabetic drugs on brain mitochondria and their association with the development of Alzheimer's disease.

production, increased brain mitochondrial membrane potential change, and increased brain mitochondrial ATP production, leading to a decrease in cognitive decline in HFD-fed mice [39]. All of these traditional medicines contain flavonoid and phenolic compounds which have antioxidant properties, and it is thought that these properties may play an important role in the improvement of insulin sensitivity and brain mitochondrial function, leading to improved cognitive function. Data regarding the effect of traditional medicine on brain mitochondrial dysfunction and its association with a delay in the development of pre-AD in association with MetS are shown in **Table 5**.

Study model	Major findings					Refs
Animal/ interventions/ duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
HFD-fed rats/ naringin (100 mg/kg) or vehicle/20 weeks	• ↓BW • ↑Peripheral insulin sensitivity • ↑ Brain insulin signaling	• ↓ROS • ↑MMP • ↑ATP	*NOR* • ↑Recognition index *MWM* • ↑Time in target quadrant • ↑Crossing target number	N/A	Naringin reduced peripheral and brain insulin resistance, improved brain mitochondrial function, and improved cognitive function in obese-insulin-resistant rats.	[34]
HFD-fed rats/garlic extract (200, 500 mg/kg) or vehicle/3 weeks	- ↔ BW • ↑Peripheral insulin sensitivity • ↑ Brain insulin signaling	• ↓ROS • ↑MMP • ↓Swelling	*MWM* • ↓Time to reach platform • ↑Time in target quadrant	N/A	Garlic extract reduced peripheral and brain insulin resistance, improved brain mitochondrial function, and improved cognitive function in obese-insulin-resistant rats.	[20]
HFD-fed rats/*Dendropanax morbifera* (20 and 50 mg/kg) or vehicle/10 weeks	• ↑Peripheral insulin sensitivity	• ↓ROS • ↑MMP • ↑ATP	*MWM* • ↑Time in target quadrant *Y-maze* • ↑Alternation behavior • ↑Total distance	N/A	*Dendropanax morbifera* reduced peripheral and brain insulin resistance, improved brain mitochondrial function, and improved cognitive function in obese-insulin-resistant rats.	[41]
HFD-fed mice + low-dose STZ/Chinese medicine ZiBu PiYin recipe or vehicle	• ↔ BW • Peripheral insulin sensitivity	• ↓ROS • ↑MMP • ↑Mito number	*MWM* • ↑Time in target quadrant • ↑Crossing target number	• ↓Cortical insoluble Aβ42	Although Chinese medicine did not improve peripheral insulin resistance, it improved brain mitochondrial function, improved cognitive function, and reduced AD marker in T2DM rats.	[39]

Abbreviations: HFD, high-fat diet; ND, normal diet; BW, body weight; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; NOR, novel object recognition; MWM, Morris water maze; NA, not assessed.

Table 5. Potential effects of traditional medicine on brain mitochondria and its association with the development of Alzheimer's disease.

4.3. Other drugs

The other therapies such as fibroblast growth factor 21 (FGF21), hydroxytyrosol 2-(3,4-di-hydroxyphenyl)-ethanol, and mitochondrial fission inhibitors also had beneficial effects on brain mitochondrial function in HFD-fed, T2DM and AD models. Our previous study found that an endocrine hormone, FGF21, decreased metabolic disturbance, brain mitochondrial ROS production, brain mitochondrial membrane potential change, brain mitochondrial swelling, synaptic dysplasticity, and cognitive decline in rats with MetS induced by the consumption of a HFD [22]. Hydroxytyrosol 2-(3,4-di-hydroxyphenyl)-ethanol, a major antioxidant phenol in olive oil, ameliorated mitochondrial dysfunction, reduced mitochondrial carbonyl protein, and enhanced superoxide dismutase 2 expression in AD mice. However, this drug did not affect Aβ accumulation in these AD mice [46]. The mitochondrial fission inhibitor, mdivi-1, improved synaptic plasticity and was associated with improving brain

Study model	**Major findings**					**Refs**
Animal/interventions/ duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
HFD-fed rats/FGF21 (0.1 mg/kg) or vehicle/20 weeks	• ↓ BW • ↑Peripheral insulin sensitivity • ↑ Brain insulin signaling	• ↓ ROS • ↑ MMP • ↓ Swelling	*MWM* • ↓ Time to reach platform • ↑ Time in target quadrant *Synaptic plasticity* • ↑ LTP	N/A	FGF21 reduced peripheral and brain insulin resistance, improved brain mitochondrial function and cognitive function in obese-insulin-resistant rats.	[22]
APP/*PS1* mice/ hydroxytyrosol (50 mg/kg) or vehicle/8 weeks	N/A	• ↑OXPHOS I, IV • ↑ PGC1-α	N/A	↔ Aβ levels	Hydroxytyrosol improved mitochondrial function and increased mitochondrial biogenesis in T2DM mice.	[46]
db/*db* mice/mdivi-1 (50 mg/kg) or vehicle/2 weeks	N/A	• ↑Mito density • ↑OXPHOSI • ↑ ATP	*Synaptic plasticity* • ↑ LTP	N/A	Mitochondrial fission inhibitor improved brain mitochondrial function and brain synaptic plasticity in T2DM mice.	[30]

Abbreviations: HFD, high-fat diet; ND, normal diet; BW, body weight; ROS, reactive oxygen species; MMP, mitochondrial membrane potential; OXPHOS, oxidative phosphorylation; PGC, peroxisome proliferator activated receptor gamma; ATP, adenosine triphosphate; LTP, long-term potentiation; N/A, not assessed.

Table 6. Potential interventions on brain mitochondria and their association with the development of Alzheimer's disease.

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mitochondrial function and biogenesis via increasing mitochondrial density, OXPHOS I, and ATP production in T2DM mice [30]. All of these findings indicated that the SGLT2 inhibitor, vildagliptin, liraglutide, FGF21, naringin, garlic extract, and *D. morbifera* improved not only peripheral insulin sensitivity but also brain insulin sensitivity, brain mitochondrial function, and cognitive function. Hydroxytyrosol, Mdivi-1, and ZiBuPiYin improved brain mitochondrial function and cognitive function. However, only ZiBuPiYin reduced levels of AD markers, possibly resulting in improved cognitive function.

Data regarding the effect of other drugs on brain mitochondrial dysfunction and the association of this dysfunction with the development of pre-AD in the MetS condition are shown in **Table 6**. The summarized therapeutic approaches on brain mitochondria and their association with the development of AD are shown in **Figure 2**.

In addition, previous studies showed that acetylcholine (Ach) levels of AD brain were lower than that of healthy brain [6, 12]. Therefore, acetylcholinesterase inhibitors (AChEs) are commonly used for the symptomatic treatment of AD patients. Previous *in vivo* study and *clinical study* demonstrated that AChEIs have an effect on mitochondrial function (REFs). For example, (1) Donepezil (AChEI) attenuated brain mitochondrial dysfunction by reducing calcium-induced brain mitochondrial swelling and reduced mitochondrial Aβ40 and Aβ42 accumulation in AD mice, leading to improved cognitive function in AD mice [47]. (2) A clinical study by Casademont et al. showed that rivastigmin, AChEI, enhanced mitochondrial electron transport chain function as indicated by increased complex I and complex III of mitochondrial oxidation and increased enzymatic activities of complexes II, III, and IV

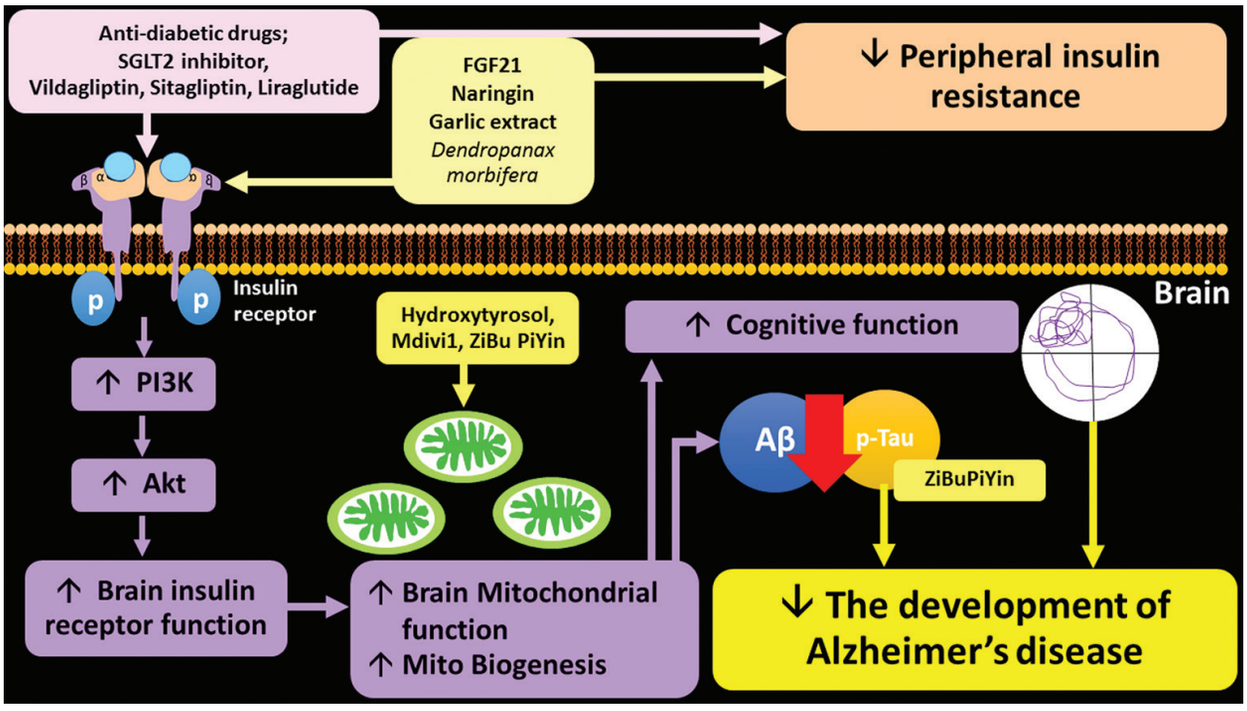


Figure 2. Summarized therapeutic approaches on brain mitochondria and their association with the development of Alzheimer's disease. Abbreviations: SGLT2, sodium-glucose transporter 2; PI3K, phosphoinositide 3 kinase; Akt, protein kinase B; FGF 21, fibroblast growth factor 21.

Study model	Major findings					Refs
Models/ interventions/ duration	**Metabolic parameters**	**Mitochondrial parameters**	**Cognitive function**	**AD marker**	**Interpretation**	
APP/PS1 (APPswe/ PS1dE9)/Donepezil (1 mg/kg) or vehicle/2 months	N/A	• ↓Ca2+ induced mitochondrial swelling	*T maze* • ↑%Accuracy *Elevated plus maze* • ↑Entry number into open arm • ↑Time in open arm	- ↓ Mito Aβ 40,42	Donepezil attenuated brain mitochondrial swelling, reduced brain Aβ accumulation, and improved cognitive function in AD mice.	[47]
AD patients/ rivastigmin (6–12 mg/ day)/6 months	N/A	• ↑Oxidation of complex I and III • ↑Enzymatic activities of complex II, III and IV • ↔Mitochondrial content	N/A	N/A	Rivastigmin enhanced mitochondrial electron transport chain function in AD patients.	[48]
Wistar rats/tacrine (15 mg/kg)/8 h	N/A	• ↓ Complex I, IV, V activity	N/A	• ↓AChE	Tacrine impaired brain mitochondrial function in rats.	[49]

Abbreviations: AChE, acetylcholinesterase; APP, amyloid beta precursor; AD, Alzheimer's disease; Ca^{2+}, calcium; Aβ, amyloid beta; N/A, not assessed.

Table 7. The effects of acetylcholine esterase inhibitors (AChEIs), the standard drugs for AD treatment, on brain mitochondrial function and their association with the development of Alzheimer's disease.

in the lymphocytes from AD patients [48]. (3) By contrast, tacrine, AChEI, impaired brain mitochondrial respiratory complex I, IV, and V activities in XX model [49]. Therefore, further studies are required to provide more evidence to support the effects of AChE inhibitor on brain mitochondrial function in AD patients as well as in the metabolic syndrome subjects. Those findings of AChEIs on brain mitochondrial function and their association with the development of Alzheimer's disease are summarized in **Table 7**.

5. Clinical implications

The presence of MetS is associated with an increase in the incidence of pre-AD. The possible underlying mechanisms involved in the association of pre-AD in MetS are still unclear. From this study, we concluded that mitochondrial dysfunction could be an important feature of AD pathogenesis in MetS. In addition, the findings indicate that the intervention which improved brain mitochondrial function led to improved cognitive function. These findings provide

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information regarding the role of mitochondria in the underlying mechanisms of pre-AD in MetS and offer important insights for future research on interventions that aim to improve the quality of life in MetS patients with AD.

6. Conclusion

In this study, the accumulated data led to the conclusion that although cognitive decline and brain mitochondrial dysfunction were observed in obese-insulin-resistant rats, AD was not developed during the pre-diabetic state. In addition, markers indicating the presence of AD were observed in T2DM subjects. Treatment with antidiabetic drugs, traditional medicine, FGF21, and mitochondrial fission inhibitors effectively improved brain mitochondrial function and cognitive function in rats with induced MetS.

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Declaration of interest

The authors declare that there are no conflicts of interest.

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