Alzheimer's disease, a metabolic disorder: Clinical advances and basic model studies (Review)

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Abstract. Alzheimer's disease (AD) is a type of neurodegenerative disease characterized by cognitive impairment that is aggravated with age. The pathological manifestations include extracellular amyloid deposition, intracellular neurofibrillary tangles and loss of neurons. As the world population ages, the incidence of AD continues to increase, not only posing a significant threat to the well-being and health of individuals but also bringing a heavy burden to the social economy. There is epidemiological evidence suggesting a link between AD and metabolic diseases, which share pathological similarities. This potential link would deserve further consideration; however, the pathogenesis and therapeutic efficacy of AD remain to be further explored. The complex pathogenesis and pathological changes of AD pose a great challenge to the choice of experimental animal models. To understand the role of metabolic diseases in the development of AD and the potential use of drugs for metabolic diseases, the present article reviews the research progress of the comorbidity of AD with diabetes, obesity and hypercholesterolemia, and summarizes the different roles of animal models in the study of AD to provide references for researchers.

Contents

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1. Introduction

Population aging is becoming a difficult problem faced by all countries worldwide, with the gradual improvement of living standards, life expectancy increases, which implies an increase in age-related diseases (1,2). Alzheimer's disease (AD) is one of the biggest obstacles to coping with a healthy aging population. AD is defined by the World Health Organization (WHO) as a neurodegenerative disease of unknown etiology, characterized by progressive deterioration of memory and cognitive function, accounting for 50-75% of all dementia cases (3,4). AD may present with clinical symptoms such as progressive memory loss, impaired executive function, difficulty in daily activities, altered thought and behavior patterns and impaired language function (5). A total of two clinical manifestations of AD are mainly recognized by the academic community: Senile plaques composed of β amyloid (Aβ) and neurofibrillary tangles composed of tau proteins with hyperphosphorylation (6). This series of processes slowly deprives the patient of memory and cognitive ability, and the patient gradually forgets recent events. The patient is unable to analyze, think and judge the events, and finds it difficult to deal with complex problems. Patients are unable to take care of themselves in daily life, making them and their family helpless over time (7,8). Although the exact process by which AD molecular cascades are triggered remains unclear, a series of epidemiological studies suggest that comorbid risk factors for metabolic disease are crucial in the pathogenesis of this disease (9-11). This suggests that physicians also associate metabolic disease with AD.

In the early nineties, some investigators noticed common mechanistic features between metabolic diseases and AD, and proposed the concept of type 3 diabetes (12-14). Researchers focused on close links between diabetes mellitus (DM) and AD, such as insulin, insulin-like growth factor, oxidative stress, glycogen synthase kinase 3β, Aβ and tau hyperphosphorylation (15-17). Since then, several studies have been carried out worldwide to explore possible links between metabolic diseases and AD, and to turn attention to AD as a type 3 diabetes; therefore, new therapeutic options for AD are explored from the perspective of metabolic disease (13,18,19). In light of recent research, it has become increasingly apparent

that AD and various metabolic diseases exhibit numerous common characteristics.

However, the mechanism by which metabolic diseases affect the progression of AD remains unclear and the selection of therapeutic drugs and animal models for AD remains to be further discussed. Moreover, the relevant literature has not been fully reviewed at present. In the present study, using 'Alzheimer's disease', 'metabolic disease', 'obesity', 'hypercholesterolemia' and 'animal model' as keywords, four electronic databases such as Springer (https://link.springer.com/), PUBMED (https://pubmed.ncbi.nlm.nih.gov/), ScienceDirect (https://www.sciencedirect.com/search) and Wiley (https://onlinelibrary.wiley.com/), were searched for relevant literature. The present article systematically discusses the research progress of metabolic diseases and the pathogenesis of AD, and summarizes the different roles of animal models in AD research, to provide a reference for researchers (for the use of acronyms see Table I).

2. Metabolic diseases and AD

Diabetes and AD. DM is the most common metabolic disorder and the direct cause of its occurrence is usually due to defective insulin action or insufficient insulin secretion (20,21). Several real-world clinical cases suggest that brain-related mild cognitive impairment complications in diabetes may lead to cognitive deficits, which gradually develops into AD (22,23).

To date, several groups have focused on exploring and explaining the link between DM and AD. Based on anatomy, some parameters showed that the Alzheimer-like pathology of diabetic rats is increased; these parameters include increased levels of Aβ plaques in the hippocampus and frontal cortex, reduced hippocampal volume, reduced protein levels in the cerebral cortex and reduced dendritic spine density in diabetic animals (24,25). Similarly, clinical evidence suggests that amygdala and hippocampal volumes in patients with diabetes are altered compared with normal patients, with a trend toward decline (26).

From a pathological perspective, the cleavage of amyloid precursor protein (APP) and the formation of Aβ plaque requires the involvement of β-secretase, which also regulates the cleavage of insulin receptor, this strengthens the link between AD and diabetes mellitus (27,28). Furthermore, soluble (s)APPβ, a product of β-secretase, is a major determinant of insulin resistance (29). Glycotoxicity can lead to structural and functional damage of brain cells and nerves, cerebral vascular hemorrhage and increased β-amyloid protein accumulation (30). These are potential mechanisms of diabetes-related dementia.

From a molecular mechanistic perspective, it has been suggested that the protein kinase A system (cAMP/PKA) signaling pathway and insulin-degrading enzyme may contribute to the type 2 diabetes-accelerated AD pathological process by causing Aβ accumulation and neuronal apoptosis (31). In addition, studies focused on protein phosphorylation have demonstrated that overexpression of protein kinase Cα (PKCα) is associated with insulin signaling interfering with insulin receptor substrate (IRS)-1 and Akt phosphorylation in skeletal muscles (32-34). PKCα inhibits insulin signaling through the IRS-Akt pathway, and inhibition and silencing of PKC-α enhances insulin sensitivity by increasing GLUT-4 translocation to the plasma membrane and glucose uptake (32). The aforementioned results demonstrate the role of PKCα in regulating neuronal insulin resistance and diabetes and open new avenues for the treatment of metabolic disorders and neurodegeneration (34). P38γ signal transduction is characterized by its unique reciprocal regulation of the phosphatase protein tyrosine phosphatase H1 antibody, and by its direct binding to promoter DNA, which is also involved in the pathogenesis of diabetes and AD, suggesting its potential as a therapeutic target (35).

Several prospective trials have used sodium-glucose co-transporter-2 (SGLT2) inhibitors (is) as an anti-diabetic drug (36,37). Inhibition of SGLT2, which accounts for ~90% of glucose reabsorption, leads to a significant reduction in blood glucose levels (36). The activation of insulin signaling associated with neuronal survival, in particular the canonical pathway of Nev (pIR, pY-IRS-1, Pakt), has been demonstrated (36). In addition, brain magnetic resonance spectroscopy has been used to detect decreased concentrations of the excitatory neurotransmitter glutamate and its precursor glutamine after administration, given that glutamate excitotoxicity has been consistently associated with AD pathology (37). These findings may inspire the reuse of anti-diabetic drugs (such as SGLT2is) in AD and other related diseases characterized by downregulation of IGF-1/insulin signaling and excitotoxicity in neurons (37). Thus, several studies conducted in this direction have shown a link between diabetes and AD (36,37), and more links between these two diseases remain to be explored.

Obesity and AD. Obesity refers to a state of being overweight or obese, often caused by excessive accumulation of fat in the body, and is closely associated with cognitive impairment and AD (38-41). Body mass index (BMI) is the most common measure of obesity worldwide. BMI is calculated as weight (kg) divided by height (m^2) squared. Obesity is defined as BMI ≥30 kg/m^2 (42,43). However, BMI does not represent regional fat distribution, which varies by sex, age, ethnicity and residential area (44). Regional fat distribution may have different effects on cognitive decline and AD-related brain changes (45). However, different regions of the fat pool may have different cognitive outcomes and have different effects on the brain.

To date, several groups have focused on exploring and explaining the link between obesity and AD. The authors classify fat as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). Hepatic fat in VAT and non-alcoholic steatosis (NAFLD) is the most studied regional fat (46). Researcher has used MRI and functional MRI for structural brain measurements to assess the strong association between obesity and brain changes in different regions (47). A study has demonstrated that increased VAT is associated with decreased grey matter density and cognitive function and that such a relationship is age-dependent (48). For patients with NAFLD, hepatic fat deposits are significantly associated with smaller overall brain volumes as well as smaller cingulate and hippocampal volumes (49). Even after weight loss, NAFLD is still associated with smaller total brain volume (50). Structural measures indicate that higher VAT and SAT are associated with smaller total brain volumes (51). Elevated VAT is

Table I. Abbreviation table.

Full name	Abbreviation
Fludeoxyglucose	18F
Alzheimer's disease	AD
Apolipoprotein E	APOE
Amyloid precursor protein	APP
β amyloid	Aβ
Blood-brain barrier	BBB
Body mass index	BMI
Protein kinase A system	cAMP/MPK
Diabetes mellitus	DM
Endogenous melatonin reduction	EMR
18F-fludeoxyglucose	FDG
Hypercholesterolemia	FH
Hypercholesterolemia	HC
Insulin-degrading enzyme	IDE
Insulin receptor	INSR
Low-density lipoprotein	LDL
Mild cognitive impairment	MCI
m.p Eparviflora leaf hydroalcoholic extract	MpHE
Magnetic resonance spectroscopy	MRS
Non-alcoholic steatosis	NAFLD
Neurofibrillary tangle	NFT
Positron emission tomography	PET
Soluble APP β	sAPP β
Subcutaneous adipose tissue	SAT
Sodium-glucose CO-TRANSPORTER-2 inhibitors	SGLT2is
Thy1-C/EBP β transgenic mice	TG mice
Visceral adipose tissue	VAT

associated with cortical thinning, particularly with decreased hippocampal volume (52). The aforementioned study showed that higher VAT is associated with higher brain network damage in cognitive decline, suggesting a strong link between VAT and accelerated brain ageing.

From a pathological point of view, existing experimental results compare individuals with higher VAT metabolism (higher metabolic capacity of visceral adipose tissue) with individuals with lower VAT metabolism (lower metabolic capacity of visceral adipose tissue) (53,54). Individuals with higher VAT metabolism have been found to exhibit higher brain Aβ levels, suggesting a close relationship between VAT dysfunction and AD disease development (53). In addition, another study using brain 18F-fludeoxyglucose positron emission tomography (PET) as a neurodegenerative biomarker of AD yielded the same results (54).

Analyzed from a possible molecular mechanism standpoint, potential factors related to brain changes and cognition may be explained by the release of different secretory factors from different fat deposits (55,56). These different fat deposits release different secreted factors that can cross the blood-brain barrier (BBB) and cause damage, increase cognitive impairment and accelerate AD progression (55). Pro-inflammatory factors secreted by adipocytes, such as leptin, IL-6 and TNF-α, can cross the BBB and lead to neuroinflammation, thus playing a role in cognitive impairment and AD (56). Another study showed that a high-fat diet stimulates diabetes and insulin resistance in Thy1-C/EBPβ transgenic (TG) mice, with significant Aβ accumulation and hyperphosphorylation of Tau protein in the brain, triggering cognitive impairment (57). A study investigated the anti-inflammatory effects of *M. parviflora* leaf hydroalcoholic extract (MpHE) on obese mice with AD, showing that MpHE effectively reduces astrocyte proliferation, the presence of insoluble Aβ peptides in the hippocampus and spatial learning impairment in lean and obese 5XFAD mice (57). Furthermore, a study investigated the association between AD and obesity from the perspective of the gut microbiota. Endogenous melatonin reduction can cause systemic changes mediated by dysbiosis of the gut microbiota, which may be one of the causative factors of AD and obesity (58). Thus, several studies in this direction demonstrate a link between obesity and AD, and more links between these two diseases remain to be explored.

Hypercholesterolemia and AD. Familial hypercholesterolemia is a particularly severe type of hyperlipidemia. The clinical features were hypercholesterolemia, characteristic xanthoma and family history of early-onset cardiovascular disease (59). Patients have abnormally high levels of low-density lipoprotein (LDL) cholesterol, which is 4-6 times higher in patients with homozygous LDL cholesterol compared with in normal individuals (60). Animal studies showed that diet-induced hypercholesterolemia increases the accumulation of Aβ and accelerates the pathological process of AD (61).

To date, several research groups have focused on exploring and explaining the association between hypercholesterolemia and AD. The researchers used fludeoxyglucose (18F) PET to study different populations, revealing common anatomical structures between individuals at risk for hypercholesterolemia and AD (62-65). The analysis showed that higher serum total cholesterol levels are associated with lower bilateral CMRgl in areas of the anterior cuneiform, parietal-temporal and prefrontal lobes previously found to be preferentially affected by AD, as well as other frontal regions previously found to be preferentially affected by normal aging (65). In certain brain regions affected by AD, the association is greater in apolipoprotein E (APOE)-4 carriers compared with in non-carriers (66). A study showed that higher serum total cholesterol levels in middle age would accelerate brain processes associated with normal aging and act in concert with other risk factors for AD predisposition (67).

The APOE gene is the strongest genetic risk factor for AD, accounting for 60-80% of all dementia cases (68,69). APOE plays an important role in lipid transport and metabolism, accounting for ~7% of phenotypic variation in serum total cholesterol and 14% of polygenic variation (68). APOE also contributes ~1-8.3% of phenotypic variation and 16% of genetic variation in LDL cholesterol (70). Compared with non-carriers, APOE4 carriers tend to have higher total and LDL cholesterol as well as lower HDL cholesterol levels (71). Furthermore, higher levels of total and LDL cholesterol are associated with greater deposition of neuropathological markers of AD in the

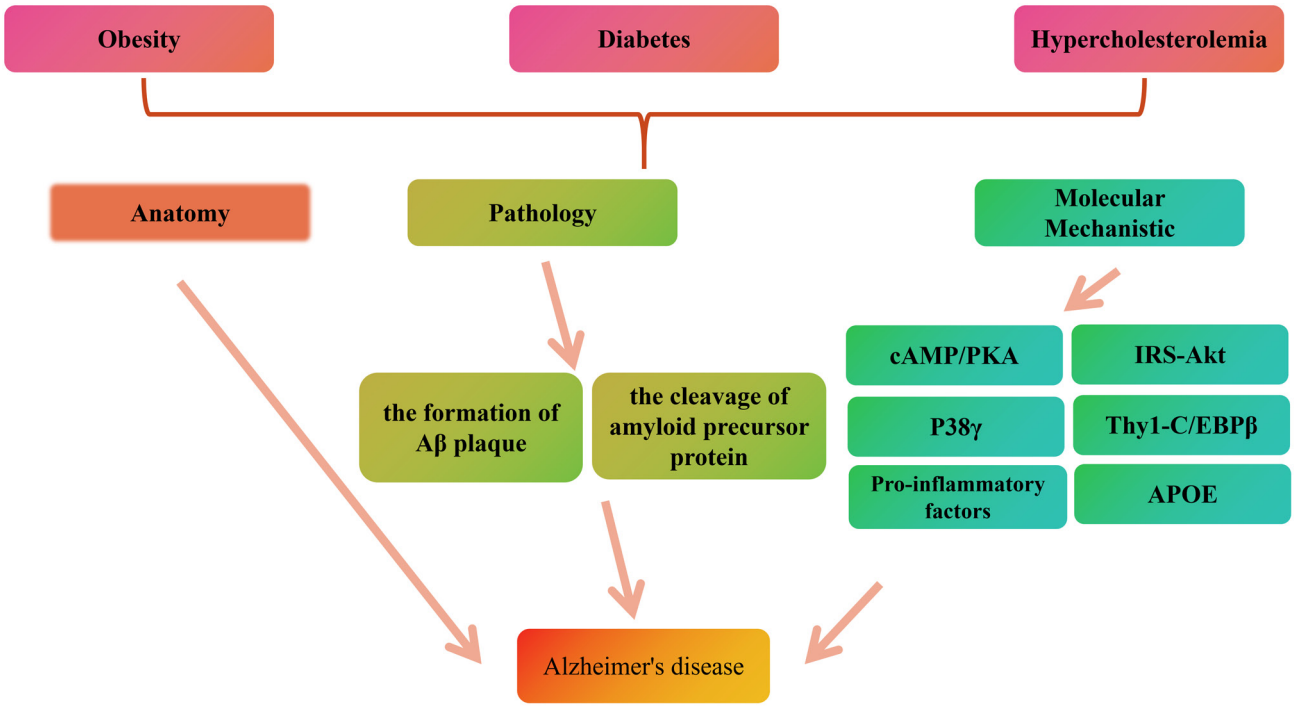

Figure 1. Role of metabolic diseases in the pathogenesis of AD. The current study reviews the research progress on AD, with regard to diabetes, obesity and hypercholesterolemia comorbidity, and analyzes it from the aspects of anatomy, pathology and molecular mechanic, among others. Aβ, β amyloid; cAMP/PKA, protein kinase A system; IRS, insulin receptor substrate; APOE, apolipoprotein E; AD, Alzheimer's disease.

cerebrum (72). Given that lipids in APOE4 carriers are most sensitive to diet, these findings suggested that lipid management through dietary adjustment can reduce AD risk (73). Menopause itself is associated with a more adverse lipid profile compared with premenopause, especially for APOE3 and APOE4 carriers. Furthermore, APOE4-related AD risk is stronger in females compared with in males (74).

A reasonable mechanism by which diet and lipids may contribute to dementia pathology is by altering levels of oxymethanol, the oxidized product of cholesterol (75). Dyslipidemia and dietary cholesterol intake may result in unbalanced oxidant levels, which appear to result in an unbalanced oxidative type of reduction (75). Studies in mice further support the possibility of reducing AD risk through dietary adjustment. For example, mice fed with a high-cholesterol diet subsequently have higher levels of total cholesterol in plasma and Aβ protein in the brain compared with controls (76). Similarly, a high-fat diet results in greater Aβ deposition and impaired neuroinflammation, sensorimotor function and social interaction, as well as a tendency for APP/PS1 mice to have poorer short-term memory compared with mice fed a control diet, but this trend was not significant (77). Thus, several studies conducted in this direction showed a link between hypercholesterolemia and AD, and more links between these two diseases remain to be explored.

3. Application of animal models in AD

To find effective therapeutic measures, researchers construct different animal models based on pathogenesis, but different animal models of AD have different advantages and disadvantages (76,77).

Human beings and animals have great similarities in physiology and pathology. It is a common research method to simulate disease in animals to explore its biological mechanism. In the research history of AD, common AD model-making animals include *Caenorhabditis elegans, Drosophila melanogaster*, zebrafish, mice, rats, dogs, rhesus monkeys and chimpanzees, among others (78,79).

These experimental animals differ in species and conditions, each with different strengths and weaknesses. For *Caenorhabditis elegans*, *Drosophila melanogaster* and zebrafish, their small size and short life span make them convenient for researchers to reproduce and manipulate, but their brain structures differ considerably from those of humans and lack high-level cognitive behavior (80,81). For rhesus monkeys and chimpanzees, these mammalian primates have the most human-like brain structures and are ideal for receiving sensory tasks that mimic cognitive impairment. At the same time, rhesus macaques and chimpanzees as animal models are expensive and their use requires careful ethical consideration (82,83). Canines are also ideal animal models, which can exhibit age-related cognitive impairment similarly to humans, but canines do not present with neural plaques and tangles (84). Mice and rats are the most economical choice in most laboratories. They have similar mammalian physiology, similar brain structure to humans and lower feeding costs. However, their selection is not perfect, and they must face the disadvantages of a long breeding cycle and high time cost (85,86). Nevertheless, mice and rats are preferred animal models in most brain science laboratories (for a classification of artificial intervention AD animal models see Table II) (87-95).

Table II. Classification table of artificial intervention AD animal models.

Model	Animal	Chemical substances/ physical methods	Method of operation	Injury site	Advantages	Disadvantages	(Refs.)
Cholinergic injury model	Wistar rat/ SD rat	Physical damage	Cholinergic injury	Hippocampal fimbria	Simulate cholinergic system damage, spatial orientation and memory impairment	No Aβ and tau pathology	(87)
Common carotid artery ligation model	SD rat/C57BL/ 6Jmice	Physical ligation	Common carotid artery ligation	Carotid artery	Chronic cerebral ischemia, cognitive, impairment	No Aβ and tau pathology	(88)
Aβ injection model	BALB/c mice	Aβ1-42	410 pmol, 3 μl brain localization injection, injection time 1 min, needle retention 3 min	Lateral ventricle (0.5 mm behind bregma point, 1.0 mm lateral to midline, 2.5 mm in depth)	-	-	(89)
	SD rats	AB1-40	1 g/l,1 μl, brain localization injection, injection time 5 min, needle retention 5 min	The dorsal side of the hippocampal dentate gyrus (3.3 mm posterior to the bregma, 2.0 mm lateral to the right, 3.0 mm below the dura mater, and the incisor hook plane is 2.4 mm below the interaural line)	AB deposition, inflammation, learning and memory impairment	Does not meet the characteristics of the progressive onset of AD, AB accumulates as the injection site	
	SD rats	AB25-35	10 μg/μl, brain localization injection, 1 μl each on the left and right, after 5 min injection, keep the needle for 5 min	CA1 area of the hippocampus on both sides (the bregma is the zero point, the puncture point is 3.5 mm behind the bregma, 2 mm on the right side of the midline, and the needle is vertically inserted 3 mm from the brain surface with a micro syringe)	-	-	

Table II. Continued.

Model	Animal	Chemical substances/ physical methods	Method of operation	Injury site	Advantages	Disadvantages	(Refs.)
IBO infusion model	SD rats	IBO	5 μg/μl, 1 μl	Meynert basal nucleus (1.0 mm behind bregma, 3.0 mm next to midline, 7.3 mm deep)	Aβ deposition and tau protein increase, and memory impairment	No neurofibrillary tangles	(90)
Streptozotocin infusion model	Long Evans rats	STZ	40 mg/kg, injection time 3 min	In both sides of the brain (1.0 mm behind the bregma, 1.0 mm lateral to the right side of the midline, 2.5 mm below the skull)	Aβ deposition, tau protein hyperphosphorylation, cholinergic loss, oxidative stress	No neurofibrillary tangles and senile plaques	(91)
D-gal infusion model	Swiss albino mice	D-gal	150 mg/kg, once a day, continue injection for 42 days	Subcutaneous injection/intraperitoneal injection	Tissue oxidative stress and inflammation, cognitive and cholinergic system disorders, tau protein hyperphosphorylation	No Aβ, neurofibrillary tangles and senile plaques	(92)
Aluminum trichloride infusion model	Wistar rats	Aluminum trichloride	100 mg/kg, continuous injection for 60 day	Intraperitoneal injection	Aβ aggregation, neuronal degeneration, learning and memory impairment	Modeling time is long, central cholinergic is not reduced, NFTs are different from patients with AD	(93)
OKA infusion model	SD rats	OKA	40 ng/μl, 5 μl, injection time 5 min, needle retention 5 min	Lateral ventricle (0.8 mm posterior to the bregma, 1.5 mm lateral to the midline, 3.6 mm vertical needle insertion)	Shows Tau protein hyperphosphorylation and Aβ pathological manifestations	No neurofibrillary tangles	(94)
SCOP infusion model	Wistar rats	SCOP	0.2 ml/150 g, continuous injection for 14 day	Abdominal cavity	Space and memory impairment	No typical pathological features of Aβ, neurofibrillary	(95)

AD, Alzheimer's disease; IBO, ibotenic acid; STZ, streptozotocin; D-gal, D-galactose; NFTs, neurofibrillary tangles; SCOP, scopolamine; OKA, okadaic acid.

Injection of streptozotocin (STZ) into the lateral ventricles of animals disrupts brain energy metabolism, and it is a common method to model AD in animals with corresponding Aβ deposition, hyperphosphorylation of tau protein, abnormal cholinergic function and oxidative stress (96-98). It is worth mentioning that STZ is also the primary modeling drug for diabetes. This underscores the potential co-morbid mechanisms of metabolic disease with AD in another way.

4. Discussion

The WHO estimates that the proportion of the population of the world aged >60 years old will rise to 22% by 2050 (97,98). Emerging evidence now indicates an increasing trend in patients with AD and related age-related diseases (97). For example, in the United States, the number of patients aged ≥65 years with AD and related dementia is increasing and is expected to reach 13.9 million by 2060 (98). These epidemiological studies suggest that the decline in quality of life in older adults and the increased risk of AD and related aging-related diseases pose a serious threat to global health (Fig. 1).

As the relationship between metabolic diseases and AD deepens, it is necessary to understand the reasonable relationship between the two. The present review discusses the new role of diabetes, obesity and hypercholesterolemia in AD. Changes in the hippocampus and frontal cortex have been found in both patients with metabolic disease and those with AD, using a variety of diagnostic instruments or anatomical studies. Most of these changes occur in the volume of different brain regions and the level of cortical proteins. This series of changes points to commonalities between metabolic diseases and cognitive changes in brain injury (13,19,20,41,55-57). Another study found that long-term high-sugar and high-fat diets can induce metabolic syndrome in experimental animals, and their brain tissue can exhibit typical characteristic changes of AD (99). Excessive lipid deposition in brain tissue can induce chronic inflammation, which plays an important role in the onset of AD. Exploring safe and effective intervention measures is currently one of the urgent issues that need to be addressed in the interdisciplinary treatment of metabolic syndrome. Excessive nutrition can cause changes in the hypothalamic immune system, leading to a hypothalamic inflammatory response, The activation of pro-inflammatory factors and other pro-inflammatory molecules persists in the pathological processes associated with metabolic syndrome, indicating the importance of improving obesity and other metabolic syndromes in the treatment of AD (100,101).

From a pathological perspective, the amyloid hypothesis has long been the dominant theory asserting that AD is caused by the accumulation of Aβ protein in the brain, leading to neuronal toxicity in the central nervous system (58). Metabolic diseases also happen to influence the pathogenesis of AD from different perspectives. These metabolic diseases are involved either through a process of Aβ plaque formation or increased Aβ accumulation (21-24,67).

In addition, the aforementioned metabolic diseases also affect the course of AD through some potential mechanisms. The cAMP/PKA signaling pathway, the IRS-Akt pathway, neuronal apoptosis, neuroinflammation and oxidative stress are all factors that have been verified by several research groups; they become common ground between metabolic diseases and cognitive impairment (25-28,46-49,65-67). These commonalities lead the present authors to focus on the potential of drugs commonly used to treat metabolic diseases for the treatment of AD. There are rich pathophysiological links between AD and diabetes. It is not difficult to imagine that some anti-diabetic drugs may be used to treat AD. Among them, insulin is the most prominent example. Aβ senile plaque formation and tau protein hyperphosphorylation are the main histopathological manifestations of AD, and insulin signaling and insulin resistance play important regulatory roles (102). Research shows that insulin can protect the brains of rats from Aβ formation, thereby having beneficial effects on them (103). Another example is metformin. The effect of metformin on insulin is achieved through AMP-activated protein kinase (104). In previous experiments, metformin has been shown to reduce tau phosphorylation and prevent pathological changes in AD neurons (105).

Animal models play an important role in the study of the pathogenesis and potential treatment of AD. The present review summarizes the common animal models and their advantages and disadvantages to provide a reference for researchers. Although several groups studied the subtle link between metabolic disease and AD, several questions remain to be answered. A common question is about the causal relationship that exists between metabolic disease and cognitive impairment. The present study has a clear understanding that these two diseases usually occur together, but the sequence and causality between them are not yet supported by strong experimental results. In addition, the criteria for characterizing AD and metabolic disease in different animal models are not consistent, which makes it difficult to map to clinical patients, which requires more data.

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FL contributed to the design of the review. HL and SZ prepared the manuscript. LT, WC, GY, HG, XW and QH made substantial contributions to conception and design. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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