Chapter 11
Therapeutic Strategies for Alzheimer's Disease in the View of Diabetes Mellitus

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Abstract Recently, Alzheimer's disease (AD) is understood as "diabetes of the brain" or "type 3 diabetes." Recent clinical trials of anti-amyloid β-protein (Aβ) therapies have not proved to be successful. Thus, glucose-insulin metabolism in the brain is thought to be an alternative therapeutic target. Various types of antidiabetic drugs such as insulin, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, biguanides, and others have been reported to be effective on cognitive impairment in animal models and patients with DM or AD. Here, recent reports are reviewed. While we identified apomorphine (APO) as a novel drug that promoted intracellular Aβ degradation and improved memory function in an AD mouse model, more recently, we have revealed that APO treatment improves neuronal insulin resistance and activates insulin-degrading enzyme (IDE), a major Aβ-degrading enzyme. In this context, recovery of impaired insulin signaling in AD neurons may be a promising therapeutic strategy for AD dementia.

Keywords Alzheimer's disease · Diabetes mellitus · Insulin · Thiazolidinediones · DPP4 inhibitors · GLP-1 agonists · Apomorphine

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11.1 Introduction

Alzheimer's disease (AD) is the major cause of dementia in the elderly people, and the therapeutics for AD is the major topic in the world. At present, four drugs are approved to use for AD patients. Among them, three drugs (donepezil, galantamine, rivastigmine) are acetylcholinesterase (AChE) inhibitors, and one is a glutamate antagonist, memantine. All these drugs have effects to slow the progression of dementia but not to improve cognitive function persistently (symptom-modifying drugs). Thus, many pharmaceutical companies and researchers have been investigating to develop novel drugs that completely inhibit disease progression and improve cognitive function (disease-modifying drugs).

To date, one of the most widely known mechanisms of AD pathogenesis has been "amyloid cascade hypothesis." There are two major pathological hallmarks of AD, neurofibrillary tangles (NFTs) and senile plaques (SPs) (Serrano-Pozo et al. 2011). NFTs consist of hyper-phosphorylated tau protein (p-tau), and SPs consist of amyloid β-protein (Aβ). Remarkably, Aβ has long been thought to play a pivotal role in the pathogenesis of AD. Because, Aβ deposition is one of the earliest phenomena in brain, followed by p-tau formation and cognitive decline (Jack et al. 2010). As shown in Fig. 11.1, Aβ is produced from Aβ protein precursor (APP) by two enzymes, i.e., β-secretase and γ-secretase. Although approximately 90% of Aβ species secreted physiologically is Aβ40, only 10% Aβ species, Aβ42, is more aggregative and forms Aβ oligomers. Aβ oligomers are more neurotoxic than Aβ monomer.

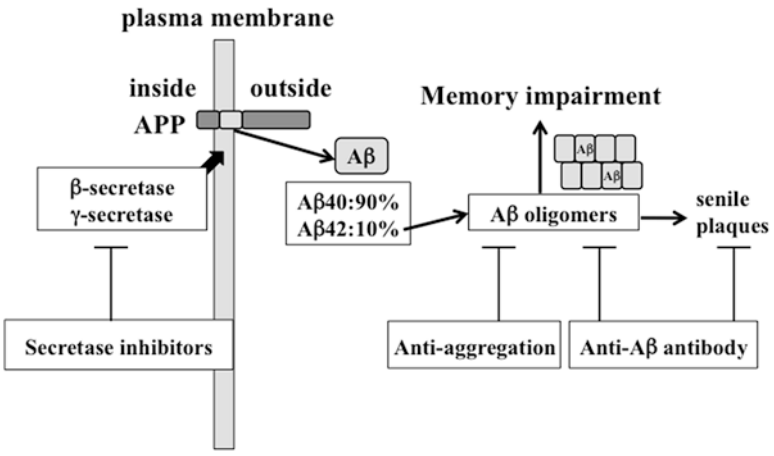

Fig. 11.1 "Amyloid cascade hypothesis" and therapeutic targets. Aβ is generated by β-secretase (β-amyloid clipping enzyme, BACE) and γ-secretase. Aβ42 takes only 10% in secreted Aβ but is highly aggregative and readily forms Aβ oligomers that are toxic for synapse and cause memory impairment. Aβ oligomers also promote hyperphosphorylation of tau protein. To attenuate this process, many inhibitors of β- or γ-secretase, anti-Aβ aggregation drugs, and immunotherapeutics such as anti-Aβ antibodies and Aβ vaccination have been developed. However, to date, almost all clinical trials of these drugs have been unsuccessful

Toxicity of Aβ may induce synaptic dysfunction leading to cognitive impairment (Ferreira et al. 2015) and may also accelerate p-tau formation (Hu et al. 2014). In addition, toxic turn Aβ42 form has recently been found (Murakami et al. 2010). Such a pathogenic cascade is named "amyloid cascade hypothesis." Based on this hypothesis, many therapeutic strategies targeting Aβ have been investigated. As shown in Fig. 11.1, β- and γ-secretase inhibitors that inhibit Aβ generation, anti-Aβ aggregation drugs, and immunological therapies using specific anti-Aβ antibodies or vaccination with Aβ peptides have been developed. Although many of these drugs were effective on AD mouse models, almost all phase III clinical trials for AD patients did not reach the primary end point. Some evidences of amyloid imaging and biomarkers in cerebrospinal fluids have been demonstrated, but cognitive impairment was not improved sufficiently (Doody et al. 2014; Salloway et al. 2014; Siemers et al. 2016). Possible causes for such unsuccessfulness are the following: (i) Aβ-targeting therapy may be effective only in preclinical and prodromal AD; (ii) sporadic AD cases in the elderly may be caused by some mechanisms different from those in AD mouse models produced by the gene engineering; and (iii) "amyloid cascade hypothesis" may not be the true mechanism in dementia of AD. As to the possibility (i), clinical trials of anti-Aβ therapy for the preclinical and prodromal AD patients are still pursued. As to possibilities (ii) and (iii), clinical trials of anti-Aβ therapy for the early-onset familial AD patients with the genes determined are now ongoing. The results of such investigation will provide us the validity of "amyloid cascade hypothesis." More recently, p-tau is focused on as a new therapeutic target other than Aβ (Boutajangout and Wisniewski 2014). However, it is unclear whether or not only the abnormal proteins accumulating in the brain are the powerful therapeutic targets to improve dementia. It is important to recover the neuronal network system improving generation of energy and metabolism in AD neurons. In this point of view, glucose-insulin metabolism may be an important therapeutic target.

11.2 Association Between Diabetes Mellitus (DM) and AD

Hypertension and DM have been widely known as the major risk factors for arteriosclerosis resulting in brain and cardiac infarction. Thus, DM has been thought to be one of the strong risk factors for vascular dementia. On the other hand, correlation between DM and AD has been investigated epidemiologically. Some reports found no correlation (Luchsinger et al. 2001; MacKnight et al. 2002; Hassing et al. 2002), but others found positive correlation between them (Leibson et al. 1997; Ott et al. 1999; Peila et al. 2002). Such discrepancies may be due to differences in determination of DM. DM was diagnosed by oral glucose tolerance tests (OGTT) in the reports that showed positive correlation but not in the negative reports. It suggests that subclinical diabetic status may contribute to AD risk. Recently, an epidemiological study in Japanese population (the Hisayama study) has clearly revealed that glucose intolerance may increase the risk of AD as well as VD in the future (Ohara

et al. 2011). In the same study, correlation between glucose intolerance and Aβ deposition (Matsuzaki et al. 2010) and DM-like gene expression patterns in the postmortem brain tissues (Hokama et al. 2014) were also demonstrated. In addition, Talbot et al. revealed an increased insulin resistance of neurons in the AD brain (Talbot et al. 2012). Taken together, increased peripheral insulin resistance, i.e., type 2 DM (T2DM), may be linked to increased neuronal insulin resistance in AD. Therefore, AD has recently been named "type 3 DM" or "brain DM" (De la Monte 2014) (Fig. 11.2). In addition, recurrent hypoglycemic attacks (Whitmer et al. 2009) and both increases and decreases in mean blood glucose levels (Crane et al. 2013) may increase the risk for dementia, indicating that marked alteration of blood glucose levels may strongly affect neuronal network function and cognitive function. Moreover, increased insulin resistance in neurons may decrease insulin-degrading enzyme (IDE), also a major Aβ-degrading enzyme (Miners et al. 2011), and may increase dephosphorylated GSK-3β, a major phosphokinase of tau protein (Avila et al. 2010), resulting in enhancing progression of the AD pathology. In this context, brain insulin resistance would be a new target in therapeutic approach for dementia in AD patients.

Recently increasing reports suggest that exercise may contribute to prevention of dementia (Barnes 2015). Also, the National Institutes of Health in the USA recommends control of T2DM, exercise habits, and healthy foods for prevention of dementia. Such recommendations may be similar to the prevention of DM. Such facts may imply a common basis of AD and DM.

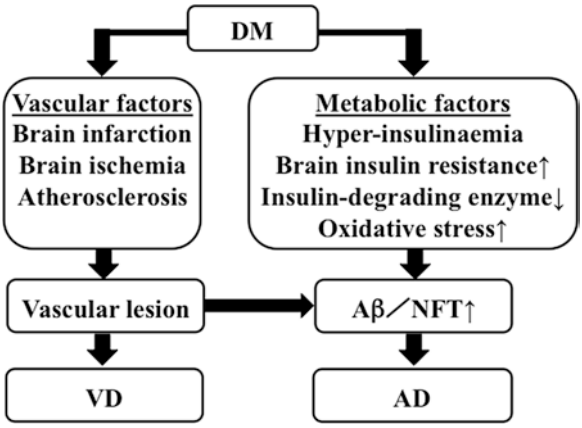

Fig. 11.2 AD pathogenesis associating with DM. DM is well known to accelerate arteriosclerosis and ischemic changes in the brain, leading to vascular dementia (VD) (left: vascular factors). While, DM may cause hyperinsulinemia, increase brain insulin resistance and oxidative stress, and decrease insulin-degrading enzyme (IDE), accelerating AD-related pathology (Aβ deposition and NFT formation). It is also known that vascular lesion due to ischemia may enhance the progression of AD pathology

11.3 Insulin Therapy

If insulin resistance is increased in neurons, insulin signaling may not work sufficiently. Insulin signaling may play a major role in signal transduction in cells, regulating cell cycle proteins (Yang and Guan 2007). Thus, first simple therapeutic strategy may be supply of insulin in AD brain. Recent reports demonstrating efficacy of insulin administration on cognitive function in rodents and human are listed in Table 11.1. In an AD model, 3xTg-AD mice ($APP_{KM670/671NL}/PS1_{M146V}/Tau_{P301L}$), high-fat diet (HFD), which increases peripheral insulin resistance, may accelerate Aβ deposition in brain and memory impairment; such phenomena may be improved by insulin injection (Vandal et al. 2014). Moreover, in these HFD-treated 3xTg-AD mice, Aβ deposition is observed in the pancreas, indicating a pathogenic self-amplifying loop between AD and T2DM (Vandal et al. 2015). More recently, many reports have demonstrated that nasal administration of insulin improved memory function, reduced Aβ deposition, increased brain-derived neurotrophic factor (BDNF) and its receptor protein tropomyosin receptor kinase B (TrkB), improved

Table 11.1 Efficacy of insulin administration

Reports of rodents	**Path**	**Subjects**	**Efficacy**
Vandal et al. (2014)	Injection	3xTg-AD	Improvement of memory function that is further impaired by HFD
Mao et al. (2016)	Nasal	APP/PS1	Improvement of cognitive function and Aβ pathology
Zhang et al. (2016)	Nasal	Anesthesia	Prevention of memory deficit and p-tau
Farzampour et al. (2016)	Nasal	Aβ injection	Improvement of memory function
Haas et al. (2016)	Ventricle	Aged rat	Increases in BDNF and TrkB receptors
Maimaiti et al. (2016)	Nasal	Aged rat	Improvement of memory and hippocampal after hyperpolarization (AHP)
Brabazon et al. (2017)	Nasal	Brain trauma	Improvement of memory and in FDG-PET
Rajasekar et al. (2017)	Nasal	STZ	Improvement of memory function and increases in Nrf-2 and BDNF expression
Kamei et al. (2017)	Nasal	SAMP8	Slowing the progression of memory loss
Reports of human	**Path**	**Subjects**	**Efficacy**
Craft et al. (2012)	Nasal	MCI/AD	Improvement of memory function
CLaxton et al. (2013)	Nasal	MCI/AD	Differential improvement of memory in male and female
Claxton et al. (2015)	Nasal	MC1/AD	Improvement of memory function especially in APOE-ε4 carriers

STZ streptozotocin, *SAMP8* senescence-accelerated mouse, *BDNF* brain-derived neurotrophic factor, *TrkB* tropomyosin receptor kinase B

hippocampal afterhyperpolarization (AHP), etc., in APP/presenilin-1 (PS1) double transgenic mice, anesthetic mice, Aβ-injected rats, aged rats, rats with brain trauma, streptozotocin (STZ)-treated rats, and senescence-accelerated mice (SAMP8) (Mao et al. 2016; Zhang et al. 2016; Farzampour et al. 2016; Haas et al. 2016; Maimaiti et al. 2016; Brabazon et al. 2017; Rajasekar et al. 2017; Kamei et al. 2017) (see Table 11.1).

While, clinical trials of nasal insulin administration to human preceded the investigation using the animal models. Craft and colleagues have demonstrated that nasal administration of insulin improves memory function in MCI and mild AD patients (Craft et al. 2012) and that such effects may be different among sex (Claxton et al. 2013) and apolipoprotein E gene alleles (Claxton et al. 2015). Insulin administered via nasal pathway did not cause systemic hypoglycemia (Craft et al. 2012; Claxton et al. 2013, 2015) and may thus seem a promising method to develop new drugs to improve the hippocampal function.

11.4 Thiazolidinediones (Glitazones)

Thiazolidinediones (glitazones) are peroxisome proliferator-activated receptor γ (PPARγ) agonists, which reduce insulin resistance of the liver and muscle. There is a possibility that these drugs improve insulin resistance of neurons in the AD brain, since neuronal insulin resistance may be increased in AD (Talbot et al. 2012). Recent reports demonstrating efficacy of thiazolidinediones (glitazones) on cognitive function in rodents and human are listed in Table 11.2. At present, there are two major glitazones, rosiglitazone (Ros) and pioglitazone (Pio). Disease models consist of some different types. First, transgenic mice with mutant APP, mutant APP + presenilin-1 (PS1) double, and mutant APP+PS1+tau triple genes were used as an early-onset familial AD models. Second, HFD- and high-fructose-diet (HFuD)-fed rats are models of T2DM, because those diets are well known to induce peripheral insulin resistance. Third, STZ-injected mouse is a model of type 1 DM (T1DM), because STZ causes selective damages in pancreatic β cells resulting in peripheral insulin deficiency. At last, congenital DM rats or mice (db/db mice) were also used. All these DM-associated mice or rats were exactly not the models of AD. However, based on the concept that AD may be "brain diabetes," drugs that improve cognitive function in these DM-associated animal models may become promising candidates for AD.

As shown in Table 11.2, Ros treatment improved memory function in HFD rats (Pathan et al. 2008), APP-Tg mice (Escribano et al. 2010), 3xTg-AD mice (Yu et al. 2015), DM rats (Ma et al. 2015), and db/db mice (Wang et al. 2016). Remarkably, Ros treatment removed the amyloid plaques and decreased p-tau in the hippocampus of APP-Tg mice (Escribano et al. 2010). Also, Pio treatment improved memory function of HFuD rats (Yin et al. 2013), STZ mice (Liu et al. 2013), 3xTg-AD mice (Yu et al. 2015), APP/PS1 mice (Toba et al. 2016), and db/db mice (Wang et al. 2016). In addition, Pio treatment prevented the β-amyloidogenic process such as Aβ

Table 11.2 Efficacy of thiazolidinediones (glitazones)

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
Pathan et al. (2008)	Ros	HFD rat	Improvement of memory function
Escribano et al. (2010)	Ros	APP	Removal of Aβ deposition
Luo et al. (2011)	Pio	HFuD rat	Inhibition of Aβ deposition process
Yin et al. (2013)	Pio	HFuD rat	Improvement of memory function
Liu et al. (2013)	Pio	STZ mice	Amelioration of memory deficit
Yu et al. (2015)	Ros, Pio	3xTg-AD	Improvement of learning and inhibition of tau phosphorylation and neuroinflammation
Ma et al. (2015)	Ros	DM rat	Improvement of memory function
Toba et al. (2016)	Pio	APP/PS1	Improvement in pre-Aβ stage in cerebellum
Wang et al. (2016)	Ros, Pio	db/db mice	Improvement of Aβ transport and enhancement of hippocampal LTP
Reports of human	**Drug**	**Subjects**	**Efficacy**
Watson et al. (2005)	Ros	MCI/AD	Preservation of cognitive impairment
Sato et al. (2011)	Pio	AD+T2DM	Improvement of cognitive function
Heneka et al. (2015)	Pio	T2DM	Decreases in risk of dementia
Chou et al. (2017)	Pio	DM	Protecting against dementia

Ros rosiglitazone, *Pio* pioglitazone, *HFD* high-fat diet, *HFuD* high-fructose diet, *STZ* streptozotocin, *T2DM* type 2 DM, *LTP* long-term potentiation

overproduction and decreased Aβ degradation induced by insulin resistance in HFuD rats (Luo et al. 2011), strengthened antioxidant defense system in HFuD rats (Yin et al. 2013), reduced brain β-amyloid clipping enzyme 1 (BACE1) in STZ mice (Liu et al. 2013). Both Ros and Pio treatments attenuated hyperphosphorylation of tau and neuroinflammation in 3xTg-AD mice (Yu et al. 2015) and promoted Aβ clearance across the blood-brain barrier (BBB) and enhanced hippocampal long-term potentiation (LTP) in db/db mice (Wang et al. 2016). In the human studies, there have been the reports indicating dementia protective efficacy of both Ros and Pio in patients with MCI/AD (Watson et al. 2005), with AD and T2DM (Sato et al. 2011), with T2DM (Heneka et al. 2015), and with DM (Chou et al. 2017), whereas some other reports indicated the negative data as to the efficacy of Ros and Pio (Miller et al. 2011; Harrington et al. 2011; Seaquist et al. 2013; Hildreth et al. 2015; Galimberti and Scarpini 2017). Further large-size clinical trials are necessary to determine their effects.

11.5 DPP4 Inhibitors

Dipeptidyl peptidase-4 (DPP4) degrades incretin hormones, which stimulate secretion of insulin from the pancreas and decrease blood glucose levels. Incretin hormones contain glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, DPP4 inhibitors enhance incretin hormone activity followed by increase in levels of plasma insulin. DPP4 inhibitors would therefore increase insulin stimulation in the AD brain. Recent reports demonstrating efficacy of DPP4 inhibitors (gliptins) on cognitive function in rodents and human are listed in Table 11.3. Currently, there are some well-known gliptins such as sitagliptin (Sita), saxagliptin (Saxa), vildagliptin (Vilda), alogliptin (Alo), and linagliptin (Lina). As well as PPAR-γ agonists, many reports indicate that these gliptins

Table 11.3 Efficacy of DPP4 inhibitors (gliptins)

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
D'Amico et al. (2010)	Sita	APP/PS1	Inhibition of Aβ deposition
Kosaraju et al. (2013a)	Saxa	STZ rat	Improvement of memory function, p-tau, Aβ burden and inflammation increasing GLP-1 in hippocampus
Kosaraju et al. (2013b)	Vilda	STZ rat	Improvement of memory function, p-tau, Aβ burden and inflammation increasing GLP-1 in hippocampus
Sakr (2013)	Sita	T2DM rat	Improvement of memory function increasing Adipo R1 expression
Pipatpiboon et al. (2013)	Vilda	HFD rat	Improvement of mitochondrial function
Sripetchwandee et al. (2014)	Vilda	HFD rat	Increases in dendritic spines in CA1
El-Sahar et al. (2015)	Sita	DM rat+ischemia	Protection against oxidative stress, inflammation, and apoptosis
Gault et al. (2015)	Sita	HFD mice	Improvement of memory function
Tsai et al. (2015)	Sita	Ischemia	Protection against chronic inflammation
Pintata et al. (2016)	Vilda	HFD rat	Improvement of cognitive function with energy restriction
Qin et al.(2016)	Alo	DM rat	Inhibition of inflammation in hippocampus
Kosaraju et al. (2016)	Lina	3xTg-AD	Improvement of cognitive function
Reports of human	**Drug**	**Subjects**	**Efficacy**
Tasci et al.(2013)	Vilda	T2DM	Inhibition of progression of cognitive impairment with metformin therapy
Rizzo et al. (2014)	DPP4I	T2DM	Protection against cognitive impairment
Isik et al. (2017)	Sita	DM±AD	Improvement of cognitive function in DIM with or without AD

Sita sitagliptin, *Saxa* saxagliptin, *Vilda* vildagliptin, *Alo* alogliptin, *Lina* linagliptin, *DPP4I* DPP4 inhibitors, *HFD* high-fat diet, *STZ* streptozotocin, *T2DM* type 2 DM

may improve memory function and mitochondrial function and inhibit Aβ deposition, p-tau deposition, and neuroinflammation (D'Amico et al. 2010; Kosaraju et al. 2013a, b, 2016; Sakr 2013; Pipatpiboon et al. 2013; Sripetchwandee et al. 2014; El-Sahar et al. 2015; Gault et al. 2015; Tsai et al. 2015; Pintata et al. 2016; Qin et al. 2016) (Table 11.3). The fact that such drugs may be effective for AD mouse models as well as for cognitive deficit in mice with T1DM (STZ) and T2DM (HFD), indicates a common mechanism in cognitive impairment in AD and DM. In human studies, although there have not been clinical trials for MCI or AD patients, DPP4 inhibitors may be beneficial to protect against cognitive impairment in patients with T2DM (Tasci et al. 2013; Rizzo et al. 2014) and may also be effective on patients with AD (Isik et al. 2017). Thus, further clinical trials of DPP4 inhibitors for AD patients are necessary.

11.6 GLP-1 Agonists

As mentioned above, GLP-1 is one of incretin hormones that stimulate insulin secretion. As well as DPP4 inhibitors, GLP-1 agonists and GIP are included in the incretin-related drugs. Recent reports demonstrating efficacy of GLP-1 agonists (glutides) on cognitive function in rodents and human are listed in Table 11.4. To date, liraglutide (Lira), lixisenatide (Lixi), exenatide (Exen), and exendin-4 (Ex-4) have been investigated using animal models. As shown in Table 11.4, many reports demonstrated that these GLP-1 agonists improved memory function and hippocampal LTP, inhibited Aβ deposition and microglial activation, and decreased insulin resistance and tau phosphorylation in HFD mice, STZ mice, APP/PS1 mice, intraventricular Aβ-injected mice, and 3xTg-AD mice (Table 11.4). Interestingly, Ex-4 treatment recovered permeability of BBB and blood-CSF barrier (BCSFB) damaged by DM, indicating a novel efficacy of GLP-1 agonists other than stimulation of insulin secretion (Zanotto et al. 2017). Remarkably, there have been much evidence for the efficacy of Lira treatment, and Lira seems to be a promising drug in the AD therapeutics. However, only a few reports have shown negative results (Egefjord et al. 2012) and a limited effect in patients with mood disorder (Mansur et al. 2017). Currently, further clinical trials for AD patients are still under investigation.

11.7 Other Antidiabetic Drugs

Recent reports demonstrating efficacy of other antidiabetic drugs on cognitive function in rodents and human are listed in Table 11.5. Sulfonylureas, biguanides, α-glucosidase inhibitors (α-GIs), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are also known as antidiabetic drugs. Sulfonylureas stimulate insulin

Table 11.4 Efficacy of GLP-1 agonists (glutides)

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
Gault et al. (2010)	Ex-4	HFD mice	Improvement of cognitive function and LTP
Porter et al. (2010)	Lira	HFD mice	Improvement of memory function
McClean et al. (2011)	Lira	APP/PS1	Inhibition of Aβ deposition
Porter et al. (2011)	GIF	HFD mice	Improvement of cognitive function and LTP
Bomfim et al. (2012)	Ex-4	APP/PS1	Recovery of insulin signaling
Ma et al. (2012)	GLP-1	APP/PS1	Improvement of memory function
Long-Smith et al. (2013)	Lira	APP/PS1	Decrease in insulin resistance and attenuation of Aβ deposition and microglial activation
Faivre and Hölscher (2013)	GIP	APP/PS1	Improvement of synaptic plasticity and reduction of numbers of Aβ plaques and activated microglias
Lennox et al. (2014a)	Lixi	HFD mice	Improvement of learning and memory and LTP in hippocampus
Lennox et al. (2014b)	GLP-1	HFD mice	Improvement of learning and memory and LTP in hippocampus
McClean and Hölscher (2014)	Lira	APP/PS1	Prevention of Aβ deposition, microglial activation, and memory impairment
Gumuslu et al. (2016)	Ex-4	STZ mice	Improvement of cognitive function and upregulation of CREB and BDNF gene expression levels
Qi et al. (2016)	Lira	Aβ mice	Attenuation of tau phosphorylation via inhibiting GSK-3β
Hansen et al. (2016)	Lira	TauP301L	Reduction of tau phosphorylation and improvement of motor function
Chen et al. (2017)	Lira	3xTg-AD	Improvement of memory and reduction of tau phosphorylation
Palleria et al. (2017)	Lira	STZ rat	Inhibition of anxiolytic and pro-depressant actions as well as memory function activating AKT pathway
Zanotto et al. (2017)	Ex-4	DM rat	Recovery of permeability of BBB and BCSFB damaged by DM
Reports of human	**Drug**	**Subjects**	**Efficacy**
Egefjord et al. (2012)	Lira	AD	A protocol of clinical trial of liraglutide with PET; no effects on Aβ deposition
Mansur et al. (2017)	Lira	Mood disorder	Improvement of cognitive function

Ex-4 exendin-4, *Lira* liraglutide, *Lixi* lixisenatide, *Exen* exenatide, *GIP* glucose-dependent insulinotropic polypeptide/gastric inhibitory peptide, *HFD* high-fat diet, *STZ* streptozotocin, *LTP* long-term potentiation, *CREB* cAMP response element-binding protein, *BDNF* brain-derived neurotrophic factor, *BBB* blood-brain barrier, *BCSFB* blood-CSF barrier

Table 11.5 Efficacy of other antidiabetic drugs

Reports of rodents	**Drug**	**Subjects**	**Efficacy**
Baraka and ElGhotny (2010)	Gliben	Aβ-injected rat	Improvement of memory function
Patel et al. (2010)	Gliben	TBI rat	Improvement of memory function
Tosun et al. (2013)	Gliben	SAH rat	Reduction of neuroinflammation and cognitive impairment
Li et al. (2012)	Met	db/db mice	Attenuation of AD-like neuropathology
Asadbegi et al. (2016)	Met	HFD rat	Protection against Aβ-mediated inhibition of hippocampal LTP
Allard et al. (2016)	Met	HFD mice	Prevention of memory impairment
Tong et al. (2015)	Acarbose	SAMP8	Effect on behavioral impairment
Yin et al. (2013)	Acarbose	SAMP8	Alleviation of memory impairment
Lin et al. (2014)	Empa	db/db mice	Amelioration of cognitive dysfunction
Reports of human	**Drug**	**Subjects**	**Efficacy**
Imfeld et al. (2012)	SU	AD	No association between SU and AD risk
Cheng et al. (2014)	SU	T2DM	Reduction of risk for dementia
Ng et al. (2014)	Met	DM	Reduction of the risk for cognitive decline
Herath et al. (2016)	Met	DM	Reduction of the risk for cognitive decline
Ye et al. (2016)	Met	DM	Reduction of the incidence rate of dementia (A meta-analysis)

Gliben glibenclamide, *Met* metformin, *Empa* empagliflozin, *SU* sulfonylurea, *TBI* traumatic brain injury, *SAH* subarachnoid hemorrhage, *HFD* high-fat diet, *HFuD* high-fructose diet, *T2DM* type 2 DM, *LTP* long-term potentiation

secretion from β-cells in the pancreas. Glibenclamide, a sulfonylurea drug, improved memory function in the rats intracerebroventicularly injected with Aβ peptide (Baraka and ElGhotny 2010) and in the rats with traumatic brain injury (TBI) (Patel et al. 2010). Also, inhibition of the Sur1-Trpm4 channel by glibenclamide reduces neuroinflammation and ameliorates cognitive impairments in rat and human with subarachnoid hemorrhage (SAH) (Tosun et al. 2013). Although glibenclamide may have protective effects on cognitive function, there have been no studies using AD mouse models. In human studies, there is a report that indicates no association between sulfonylurea and risk of AD (Imfeld et al. 2012), while sulfonylurea would reduce the risk for dementia in T2DM patients (Cheng et al. 2014). Since hypoglycemic attacks may increase the risk for dementia (Whitmer et al. 2009), evaluation of the efficacy of sulfonylurea should be carefully investigated.

Biguanides inhibit glycogenesis in the liver and uptake of glucose from the intestine and improve insulin resistance. A well-known biguanide metformin was reported to attenuate tau phosphorylation in db/db mice (Li et al. 2012) and to have protective effects on cognitive function in combination in HFD mice (Asadbegi et al. 2016; Allard et al. 2016). In human, it is suggested that metformin treatment reduced the risk of cognitive decline in DM patients (Ng et al. 2014; Herath et al. 2016). Also, a meta-analysis suggests that metformin and thiazolidinediones may reduce the incidence rate of dementia with the relative risks, 0.79 and 0.75,

respectively (Ye et al. 2016). Efficacy of biguanides for AD patients should be evaluated in the future studies.

α-GIs inhibit postprandial hyperglycemia and would thus inhibit glucotoxicity in the brain. Although there have been no reports of investigation about efficacy on rodents or patients with AD, chronic acarbose treatment may have a protective effect on behavioral impairment (Tong et al. 2015) and alleviated memory impairment (Yan et al. 2015) in SAMP8 mice. The efficacy of α-GIs for the cognitive impairment in DM and AD remains to be elucidated.

SGLT-2 inhibitors are newcomers in antidiabetic drugs. These drugs inhibit reuptake of glucose in the kidney and lower the blood glucose level. Since the term of usage of SGLT-2 inhibitors is not long, there have been few reports studying about its efficacy on cognitive impairment. A recent report demonstrated that empagliflozin treatment ameliorates cardiovascular injury and cognitive dysfunction in db/db mice (Lin et al. 2014). At present, many SGLT-2 inhibitors are used for control of blood glucose levels. Thus, further investigation about its efficacy should be continued.

11.8 Apomorphine (APO)

Lastly, we describe about our recent finding of novel efficacy of apomorphine (APO) for AD. Although APO is well known to be a dopamine agonist for patients with Parkinson's disease (PD), we have recently found efficacy of APO for cognitive improvement in AD and have also found APO to be effective on brain diabetes.

In the beginning of this century, based on many studies using AD mouse models produced by mutant APP and PS1 genes, anti-Aβ therapies such as Aβ vaccination and anti-Aβ antibodies were thought to be a promising therapeutic strategy for AD. However, it is well known that many clinical trials targeting Aβ in AD patients have failed. While, our previous studies first revealed that oxidative stress-related apoptosis stimulation induced intracellular Aβ42 deposition in contrast to reduction of extracellular Aβ secretion in primary neuronal cultures (Ohyagi et al. 2000). Subsequently, we found intracellular accumulation of Aβ42 to promote the p53 mRNA expression resulting in neuronal apoptosis (Ohyagi et al. 2005). In addition, intracellular Aβ42 was reported to promote apoptosis via various pathways (Ohyagi 2008). Therefore, we did search for novel drugs that may promote intracellular Aβ42 degradation. Using SH-SY5Y cells, we established an assay system for intracellular Aβ degradation and found that treatment with APO, which has been suggested to protect neurons from oxidative stress in PD mouse models and from brain infarction in a gerbil stroke model (Mandel et al. 2004; Castri et al. 2006), accelerated Aβ42 degradation through activating insulin-degrading enzyme (IDE) and proteasome system (Himeno et al. 2011). Furthermore, APO therapy improved memory function and the AD pathology in 3xTg-AD mice (Himeno et al. 2011) (Fig. 11.3).

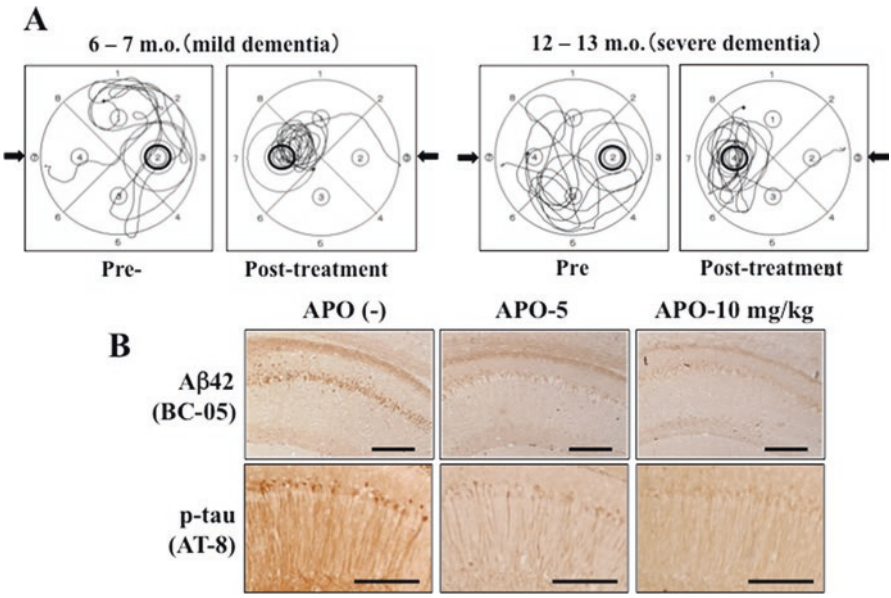

Fig. 11.3 Efficacy of APO on 3xTg-AD mice (Himeno et al. 2011; Nakamura et al. 2017). (**a**) Morris water maze (MWM) of the representative 3xTg-AD mice treated with APO. 6-month-old and 12-month-old mice were subcutaneously injected with 5 m/kg APO once a week for 1 month (total five times). After memorizing the platform location, track of 60 s free swimming was analyzed. Both 7- and 13-month-old mice exhibited improvement of spatial memory posttreatment compared to pretreatment. (**b**) Immunohistochemistry of hippocampus CA1 in 7-month-old mice. Both Aβ42 and p-tau levels were lower in APO-treated mice compared to untreated mice. Bars = 100 μm

Further investigation has revealed that APO treatment may enhance intracellular antioxidative stress system protecting cells from apoptosis (Ma et al. 2011). In addition, DNA microarray analysis has revealed that APO treatment may effect on regulation of cell cycle, which is a quite different characteristic from other kind of dopamine agonists, and upregulates molecules relating to insulin signaling (unpublished data). Taken together, we hypothesized that APO treatment may upregulate IDE through activating insulin signaling. In our recent report (Nakamura et al. 2017), western blotting and immunostaining revealed that IDE was upregulated and two types of serine-phosphorylated insulin receptor substrate-1 (pS^{616} and $pS^{636+639}$ IRS-1) were downregulated in APO-treated 3xTg-AD mice brain. Figure 11.4 shows immunostaining data of hippocampus (CA1) in 13-month-old mice in that report (Nakamura et al. 2017). IDE was increased in 3xTg-AD mice compared to non-Tg mice and was further increased by APO treatment, while Aβ was decreased by APO treatment (Fig. 11.4a). In the same 13-month-old mice, pS^{616} and $pS^{636+639}$ IRS-1 were increased in 3xTg-AD mice compared to non-Tg mice and were decreased by APO treatment (Fig. 11.4b). All the alterations were statistically significant (Fig. 11.4a, b, right panels), indicating that APO treatment may decrease

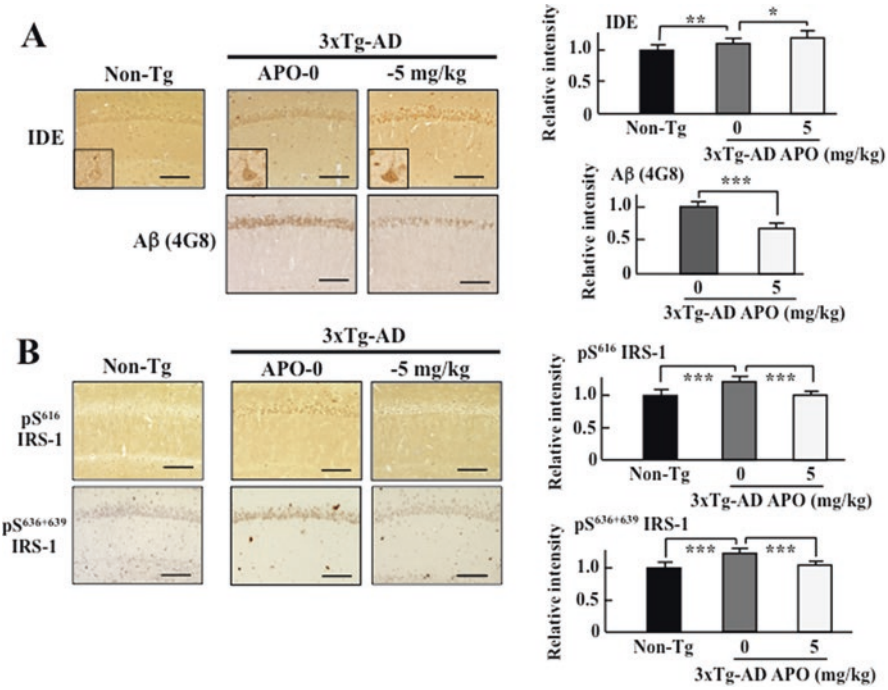

Fig. 11.4 Quantitative analysis of immunohistochemistry of hippocampus CA1 (Nakamura et al. 2017). (**a**) IDE and Aβ. IDE is increased in 3xTg-AD compared to non-Tg mice. APO treatment further increased IDE level. In contrast, Aβ is decreased by APO treatment. Inset shows a solitary neuron. (**b**) pS^{616} and $pS^{636+639}$ IRS-1. Both types of IRS-1 are increased in 3xTg-AD mice compared to non-Tg mice and are decreased by APO treatment. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Bars = 100 μm

insulin resistance of neurons (decreases in pS^{616} and $pS^{636+639}$ IRS-1) and may enhance insulin signaling associating with IDE upregulation.

Since APO is currently used as a subcutaneous injection drug for PD patients, we checked its effects on five AD patients without DM and have observed slight improvement of memory function (unpublished data). Also, APO treatment may reduce Aβ burden in the brains of PD patients (Yarnall et al. 2016). Thus, APO may be effective on "brain diabetes" as ~~well as~~ PPAR-γ agonists, DPP4 inhibitors, and GLP-1 agonists. In Fig. 11.5, our hypothesis of molecular pathogenesis in AD brain and therapeutic targets of APO therapy are presented. In AD neurons, increased insulin resistance decreases insulin signaling, leading to decreases in IDE levels and increases in GSK-3β, which may accelerate accumulation of both Aβ and p-tau, respectively. Increased Aβ oligomers may inhibit insulin signaling, which may result in a vicious cycle. APO may activate insulin signaling and IDE and may inhibit GSK-3β, thereby inhibiting AD pathology. In this context, APO may become a novel drug for AD targeting glucose-insulin metabolism in neurons. To evaluate

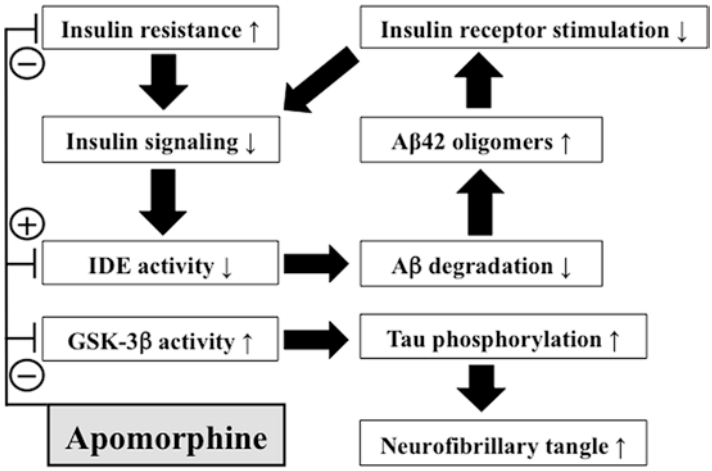

Fig. 11.5 Hypothetic scheme of pathogenesis related to insulin metabolism and therapeutic targets of APO in AD brain (Nakamura et al. 2017). Increased insulin resistance attenuates insulin signaling. Decreased insulin signaling downregulates IDE and upregulates GSK-3β, which increases Aβ oligomers and tau phosphorylation/neurofibrillary tangle, respectively. Increased Aβ42 oligomers attenuate insulin receptor stimulation, thereby fostering vicious cycle. APO treatment may improve insulin resistance, upregulate IDE, and attenuate GSK-3β activity

the significance of APO treatment, APO effects should be checked in comparison with other DM drugs in the future.

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