Metabolic Brain Disease
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REVIEW ARTICLE

Insulin resistance: a connecting link between Alzheimer's disease and metabolic disorder

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Abstract
Recent evidence suggests that Alzheimer's disease (AD) is closely linked with insulin resistance, as seen in type 2 diabetes mellitus (T2DM). Insulin signaling is impaired in AD brains due to insulin resistance, ultimately resulting in the formation of neurofibrillary tangles (NFTs). AD and T2DM are connected at molecular, clinical, and epidemiological levels making it imperative to understand the contribution of T2DM, and other metabolic disorders, to AD pathogenesis. In this review, we have discussed various modalities involved in the pathogenesis of these two diseases and explained the contributing parameters. Insulin is vital for maintaining glucose homeostasis and it plays an important role in regulating inflammation. Here, we have discussed the roles of various contributing factors like miRNA, leptin hormone, neuroinflammation, metabolic dysfunction, and gangliosides in insulin impairment both in AD and T2DM. Understanding these mechanisms will be a big step forward for making molecular therapies that may help maintain or prevent both AD and T2DM, thus reducing the burden of both these diseases.

Keywords Alzheimer's disease · T2DM · Insulin resistance · Gangliosides · miRNA · Inflammation

Introduction

Alzheimer's disease (AD) is a form of dementia and is one of the leading causes of death worldwide. The World Health Organization (WHO) estimates that at present, there are approximately 50 million cases of dementia worldwide, with 10 million new cases each year; and by 2050 this number is set to increase to 152 million (World Health Organization (WHO), fact sheets and details on dementia 2019). The exact pathogenesis of AD is ambiguous; however, amyloid-beta (Aβ) plaque deposition and tau protein hyperphosphorylation are considered as the leading causative factors for AD pathogenesis (Bloom 2014; Selkoe and Hardy 2016). Aβ deposits and hyperphosphorylated tau increase the formation of neurofibrillary tangles (NFTs), which are the pathological hallmarks of AD. Owing to these findings, Aβ and tau protein targeting have been the main focus for developing AD therapy in recent years. However, AD is difficult to diagnose at an early stage as the disease begins 20 years before the symptoms arise (Alzheimer's association 2019). It is usually diagnosed based on the person's medical history, history from relatives and behavioral observations. The presence of characteristic neurological and neuropsychological features and the absence of alternative conditions are supportive. Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI) and with single-photon emission compound tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathologies or subtypes of dementia (Alzheimer's association 2019). 18-Fluorodeoxyglucose (18-FDG) PET scan is the standard approach to assess glucose metabolic impairment in brain (Daulatzai 2012; Schaffer et al. 2015). The present pharmacological treatment for AD is palliative, none of the available medications slow or stop the progression of the disease. There are six drugs approved by the US Food and Drug Administration (FDA) for the management of AD – acetylcholinesterase inhibitors like tacrine, rivastigmine, galantamine, and donepezil, and memantine combined with donepezil and memantine, which is an N-methyl-D-aspartate (NMDA) receptor antagonist. A new way to maintain the worsening of AD is being followed through lifestyle changes

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and exercises. Especially aerobics and a combination of aerobics with normal exercises showed improved memory and slowed the memory decline in AD patients. Computerized memory training, usage of lights to better the sleep patterns of AD patients along with musical therapy is being practiced in healthcare centers (Alzheimer's association 2019). Risk of AD can also be reduced by smoking cessation, avoiding chronic alcoholism, weight control and diet control, maintaining healthy cholesterol, blood pressure, and blood glucose levels. A healthy diet has all the nutrients in balanced amounts and red meat, saturated fats and sugar should be limited. Depression, isolation, cognitive inactivity, and low education level can also affect the occurrence of dementia (World Health Organization (WHO), fact sheets and details on dementia 2019). Thus, a new method of non-pharmacological therapies is also being utilized for the management of people with AD.

Type 2 diabetes mellitus (T2DM) is an extremely common lifestyle disorder which is caused due to a sedentary and unhealthy lifestyle. Obesity is also associated with T2DM and the occurrence of one increases the risk of incidence of the other (Tripathy 2018). WHO considers diabetes as a serious public health problem. The International Diabetes Federation (IDF) estimates that 463 million adults were living with diabetes in 2019 worldwide and the number has more than tripled in the last two decades (IDF 2019). T2DM is a complex metabolic condition characterized by chronic hyperglycemia associated with insulin impairment, specific organic complications, and cardiovascular disorders (CVD) (Classification of diabetes mellitus. Geneva: World Health Organization 2019). The Rotterdam study was the first to give the initial epidemiological evidence connecting T2DM and other metabolic disorders to AD and dementia (Schrijvers et al. 2010). The occurrence of dementia nearly doubles in T2DM affected individuals. Recent evidence suggests that elevated serum glucose and insulin levels increase the risk of developing dementia, which is associated with cognitive decline and reduction of hippocampal volume (Kerti et al. 2013; Crane et al. 2013). It is now known that insulin does in fact have a neuroprotective effect and that it regulates synaptic plasticity (Grillo et al. 2015; Van Der Heide et al. 2005). Conventionally, insulin signaling impairment and insulin resistance are characteristic features of T2DM, obesity and other metabolic disorders (Lee et al. 2016; Li et al. 2018). Interestingly, insulin resistance is also developed in AD brains leading to a diabetes-like state in the brain. Insulin resistance developed in AD is attributed to c-Jun NH_2-terminal kinase (JNK) activation (Zhou et al. 2017).

As discussed earlier, it has recently been found that changes in diet and lifestyle could be of benefit to slow the progression of AD. Interestingly, calorie restricted diet has been reported to restrict the progression of AD and reduce Aβ levels (Lange et al. 2017). Unhealthy diet is associated with metabolic syndrome and its components including T2DM, obesity, hypertension, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD). Thus, a direct link is associated between metabolic syndrome and the onset of AD. Metabolic syndrome is an umbrella term that refers to cardiometabolic disorders like T2DM, obesity, hypertension, NAFLD, insulin resistance, dyslipidemia, etc. leading to increased risk of CVD (Ríos et al. 2014). Indeed, metabolic syndrome is linked to AD and many studies have established that metabolic syndrome increases the risk of developing AD and vascular dementia (De Sousa Rodrigues et al. 2019; Watts et al. 2013). In vivo models involving high-fat diet (HFD) and high-fructose diet showed the development of metabolic syndrome-associated AD with increased levels of serum insulin, glucose, triglycerides, and hyperlipidemia as well as energy metabolism deregulation (Agrawal and Gomez-Pinilla 2012; De La Monte and Tong 2014; Sharma et al. 2012; Yates et al. 2012). Moreover, the link between metabolic syndrome and AD has further been established in clinical and epidemiological studies that suggest a direct involvement of metabolic syndrome in the development of AD (Frisardi et al. 2010; Panza et al. 2011). A study done by Razay et al. was the first to investigate the relationship between AD and metabolic syndrome (Razay et al. 2007) using a standard criteria. Since then, many clinical and epidemiological studies have highlighted this relationship indicating that obesity (Whitmer et al. 2008), hypercholesterolemia (Solomon et al. 2009), hypertension (Nelson et al. 2014), and T2DM (Ahtiluoto et al. 2010) promote the development of AD and dementia. Insulin resistance is observed in metabolic syndrome and is the central link to AD and memory impairment (Kim and Feldman 2012). It is clear by these evidences that the common link between metabolic syndrome and AD is insulin signaling impairment and thus, forms a valuable tool in understanding the molecular mechanisms between these disorders. Therefore, it is important to comprehend the effect of insulin resistance in AD brains and its correlation to metabolic syndrome. The present review aims at providing an integrative analysis of the mechanisms of the elements involved in insulin transduction in AD brains and its effect on cognitive performance. An understanding of these mechanisms may prove beneficial to facilitate the development of new strategies for the management of both AD and other metabolic syndromes, sequentially improving the quality of life pertaining to both these diseases. Figure 1 illustrates metabolic dysfunction which is related to AD and metabolic syndrome.

Insulin signaling in AD

In this session, we have briefly discussed the mechanism of insulin signaling in normal and impaired conditions as central insulin resistance impairs memory and cognition and disrupts metabolic responses (Arnold et al. 2018). The Insulin receptor (IR) is a transmembrane tyrosine kinase receptor composed α/β subunit dimers that are linked by disulfide bonds. It consists

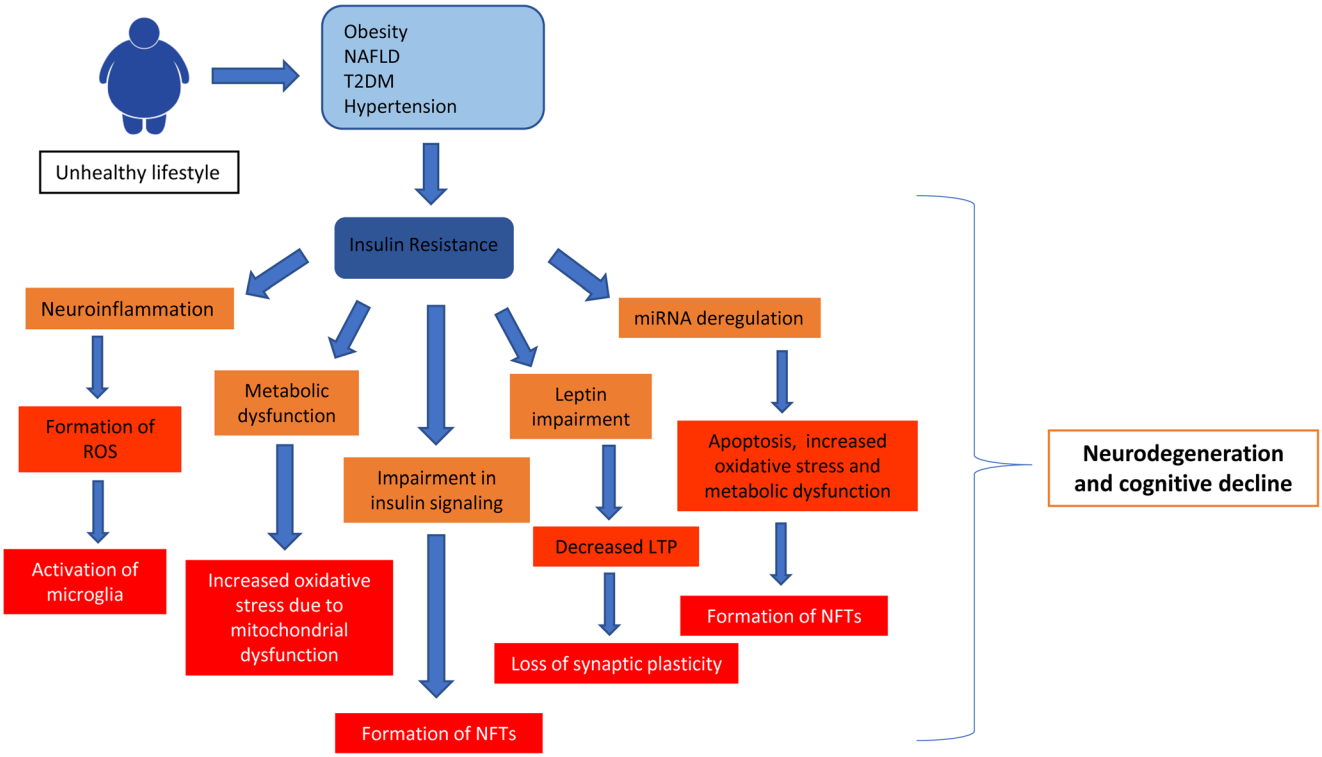

Fig. 1 Metabolic dysfunction in Alzheimer's disease (AD) and metabolic syndrome. The diagram gives an overview of different molecular mechanisms and factors that are activated by insulin resistance. Unhealthy lifestyle like calorie-rich diet and lack of exercise leads to metabolic disorders such as obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and hypertension. These metabolic disorders are associated with neurodegenerative disorders with insulin resistance playing a central role. Together with AD, these metabolic disorders are called as metabolic syndrome. Insulin resistance leads to neuroinflammation, metabolic and mitochondrial dysfunction, impairment in insulin signaling in the brain region, leptin signaling impairment, and miRNA deregulation. These factors lead to the activation of reactive oxygen species (ROS) via the activation of pro-inflammatory cytokines causing neurodegeneration. Leptin is important for maintaining long-term potential (LTP) and thus, synaptic plasticity. Centrally, insulin resistance leads to the formation of neurofibrillary tangles (NFTs) leading to AD and cognitive decline

of a transmembrane heterotetramer glycoprotein composed of two extracellular α-subunits and two membrane-spanning β-subunits. Under normal circumstances, insulin binds to the IR autophosphorylating it at tyrosine residues. This leads to the dimerization of the receptor that brings about phosphorylation of insulin receptor substrates I- IV (IRS) at specific tyrosine residues. The activated IRS complex stimulates the activation of phosphatidylinositol 3-kinase (PI3K) further leading to the activation and phosphorylation of protein kinase B (Akt). Akt acts as a major player in insulin signaling as it controls many downstream pathways that ultimately bring about the function of insulin. Phosphorylated Akt controls the activation of glucose transporter 4 (GLUT4), which is an intrinsic glucose transporter responsible for the cellular uptake of glucose. Activated Akt phosphorylates mammalian target of rapamycin (mTOR), controlling its downstream targets responsible for autophagy, growth, metabolism, and survival. Phosphorylated Akt also phosphorylates glycogen synthase kinase (GSK)-3β, thus inactivating it. GSK3β is involved in the activation of apoptotic factors like FOS, c-Jun, amyloid precursor protein (APP), and even microtubule associated tau protein. Thus, GSK3β is vital for apoptosis and maintaining long term potentiation (LTP). LTP is vital for the persistent maintenance of synapses and synaptic plasticity, thereby improving cognition and memory. By itself, Akt inhibits the expression of caspase-9 and Bcl-2 associated apoptotic factors, making it critical for cell survival. Activated IR also activates mitogen activated kinase (MAPK), which is again concerned with cell survival pathways. All these pathways are regulated by a feedback mechanism that keeps their activity in check. When IRS-1 and IRS-2 are phosphorylated at serine residues, they dissociate from the IR leading to decreased tyrosine phosphorylation of IRS, inhibiting downstream insulin signaling (Arnold et al. 2018; Vieira et al. 2018). Figure 2 illustrates insulin signaling and factors affecting it.

As previously mentioned, insulin has a neuroprotective effect and regulates synaptic plasticity and by itself is vital for optimum cognitive functioning. IR is primarily expressed in the soma and enriched in synaptic terminals of neurons in the hippocampus, amygdala, hypothalamus, cortex, entorhinal cortex, and olfactory bulb (Ronaghi et al. 2019). AD is characterized by neurodegeneration predominately in the brain regions of hippocampus and olfactory epithelium (Yao et al.

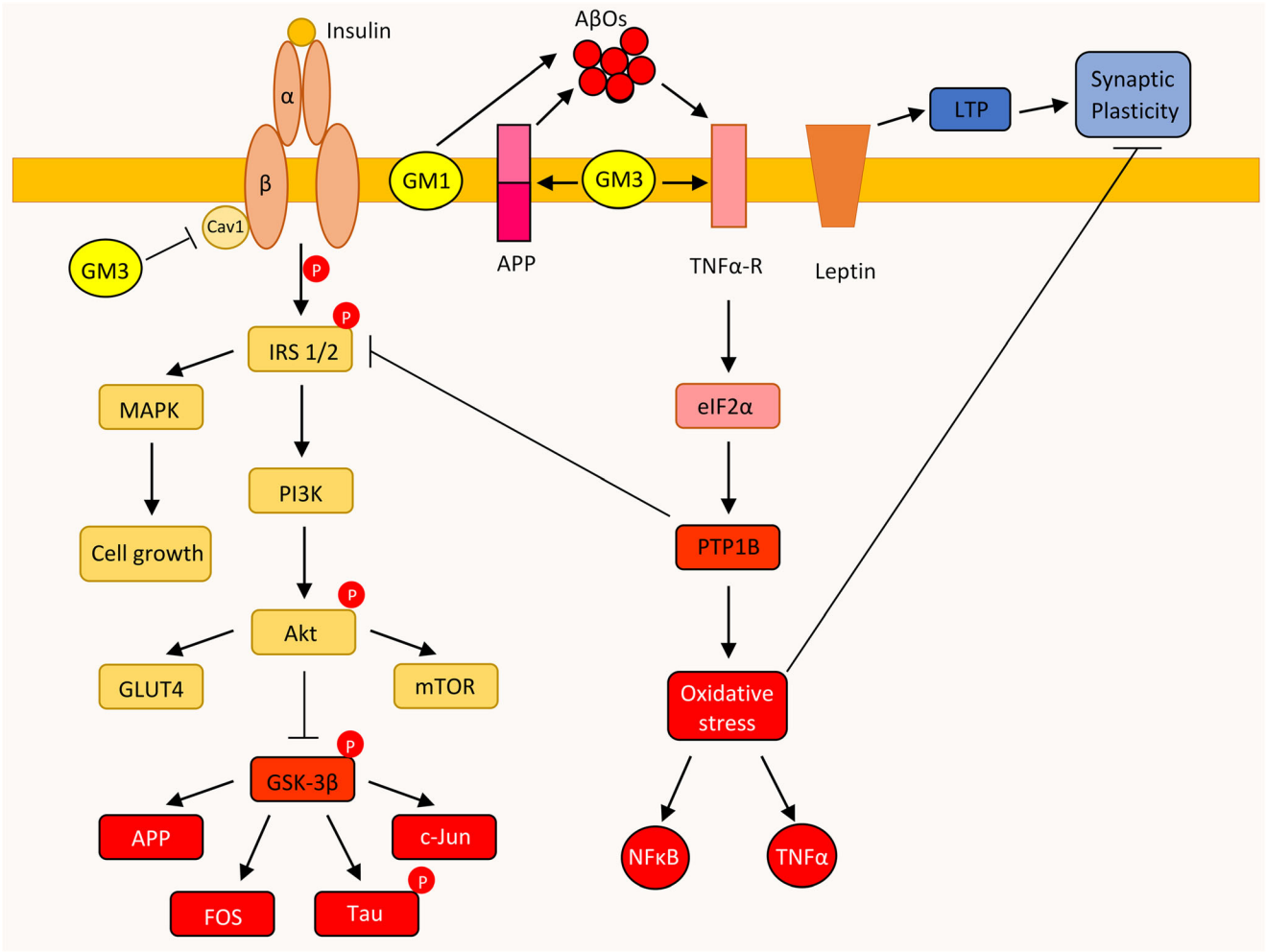

Fig. 2 Insulin signaling pathway overview and the factors affecting it. The diagram gives an overview of different mechanisms and factors that modulate insulin signaling in AD and T2DM. Under normal conditions, Akt is activated which inhibits GSK-3β and its downstream signaling. Insulin resistance results from the activation of tumor necrosis factor-alpha (TNF-α) receptor by Aβ peptides, upregulation of GM1 and GM3, dephosphorylation by protein tyrosine phosphate 1B (PTP1B), or phosphorylation of IR and IRS at serine residues. Oxidative stress plays a major role in inducing insulin resistance and impairing synaptic plasticity. Targeting these mechanisms can lead to potential therapeutic strategies for both AD and T2DM

2016). In fact, loss of smell is one of the first signs of AD because of the loss of neurons in the olfactory bulb (Velayudhan et al. 2019). Interestingly, in mammals, neurons present on the olfactory epithelium and dentate gyrus of the hippocampus are involved in the synthesis and secretion of insulin (Kuwabara et al. 2011). Indeed, mRNAs of preproinsulin 1 and 2 have been found in the neuronal cells, supporting the role of neurons in insulin synthesis (Schechter and Abboud 2001).

Insulin-dependent neuroprotection and its effect on cognition is regulated through NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors modulation; increase in sodium and calcium ions influx and reinforcing synaptic transmission (Calvo-Ochoa and Arias 2015). Moreover, it is essential that Ca^{2+} influx is mediated through the NMDA receptor for LTP (Belfiore et al. 2019). Thus, insulin functions as a neuromodulator through the activation of NMDA receptor (Van Der Heide et al. 2005). Furthermore, insulin also regulates the concentration of acetylcholine and increases the release of epinephrine and norepinephrine by inhibiting their reuptake (Rajasekar et al. 2017; Senthilkumaran et al. 2016). Insulin promotes the accumulation of $GABA_A$ receptors in the post-synaptic membranes and participates in the translation of post synaptic protein PSD-95 (Cid et al. 2008). This leads to the development of insulin resistance and the downregulation of insulin receptors in AD brains (Bomfim et al. 2012). In fact, in AD a specific form of insulin resistance is developed and hence, Alzheimer's is also being called as "type 3 diabetes." It has been shown that insulin resistance is developed by Aβ oligomers (AβO), which are proximal toxins that congregate in AD brains. Additionally, AβOs exposed to primary hippocampal neurons developed rapid insulin sensitivity, which was accompanied by marked removal of IRs from dendritic

plasma membranes by stimulating IRS-1 serine phosphorylation (Zhao et al. 2004). Collectively, this data indicates that insulin regulates the structural and functional aspects of synapse formation and potentiation.

It is important to note that phosphorylation of IR at the tyrosine residues and its downstream targets are essential for canonical insulin signaling. Phosphorylation of tyrosine residues in IR is the first step that recruits the phosphorylation of IRS-1 and its downstream targets. Indeed, PTP1B dephosphorylates tyrosine residues in IR and IRS-1, leading to the downregulation of insulin signaling (Uddin et al. 2018). Interestingly, insulin and insulin like growth factor (IGF) 1 inhibit Aβ production through Akt mediated phosphorylation or inactivation of GSK3β (Kang et al. 2017). Deficiency in the levels and activities of several components of the insulin-IRS-Akt signaling pathway leads to the activation of GSK3β, promoting hyperphosphorylation of tau (Arnold et al. 2018). Although GSK-3β phosphorylates tau, the phosphorylation of GSK3β at serine 9 by insulin inhibits its action on tau. Therefore, a reduced insulin signal increases GSK-3β activity leading to tau phosphorylation (Kang et al. 2017). It has been found that binding of AβOs to hippocampal neurons leads to the removal of IRS from the plasma membrane, leading to decreased sensitivity of IRS, insulin and IGF (Moloney et al. 2010). Remarkably, insulin and IGF1 prevent Aβ accumulation by promoting the transport of Aβ binding carrier proteins into the brain (Carro et al. 2006). IGF2 is also involved in Aβ degradation, thus exerting its neuroprotective effect (Stein and Johnson 2002).

A study showed the effect of coffee consumption on AD and T2DM (Kwok et al. 2016). It was found that coffee consumption decreased the risk of AD and T2DM; however, observational studies showed that short term consumption of coffee raises triglycerides and low-density lipoprotein (LDL) cholesterol levels. It was also observed that it may increase adiponectin and had no effect on fasting glucose, fasting insulin, or insulin resistance. Evidently, insulin resistance is exacerbated in AD and metabolic syndrome due to chronic inflammation (Rose et al. 2015). Neuroinflammation plays a vital pathological role in the development of insulin and IGF-1 resistance in AD (De La Monte and Tong 2014; Talbot 2014). Thus, insulin resistance and deficiency may symbolize a critical contributing factor to the development and progression of AD and metabolic syndrome. Some of the factors influencing it have been discussed herewith in brief.

Inflammation linking AD and metabolic syndrome

Neuroinflammation with degenerative changes in brains have been identified for years but only recently have achieved renewed interest for their involvement in AD pathogenesis. It is a known fact that peripheral insulin resistance in T2DM and metabolic syndrome drives cognitive impairment by developing central insulin resistance that is associated with neuroinflammation (Gaspar et al. 2016; Misiak et al. 2012). Formation of NFTs and beta-pleated sheets lead to the activation of microglia and immune system in AD brains. Neuroinflammation and microglial activation has long been known as an accompanying pathology of AD as evidenced by increased levels of inflammatory markers in various studies (Chowdhury et al., 2018a; Hopperton et al. 2016). Neuroinflammation increases the expression of pro-inflammatory cytokines like TNF-α, interleukin-6 (IL-6), IL-1β, macrophages, and interferon-γ around the NFT and Aβ plaques (De La Monte 2017). Additionally, neuroinflammation aids cholinergic dysfunction and promotes neuronal injury (Giovannini et al. 2002). Inflammation is also seen in metabolic disorders like T2DM and obesity. Interestingly, obesity is linked to AD via the gut-brain axis, a type of biochemical signaling node that takes place between the gastrointestinal tract and the central nervous system (Bruce-Keller et al. 2015). Moreover, it is established that gut microbiota has a substantial impact on brain functions as its decrease accentuates neuroinflammation (Neufeld et al. 2011). It is widely accepted that sustained inflammation in the peripheral tissues in metabolic syndrome leads to insulin resistance. Furthermore, accumulated fats in the adipose tissue recruit pro-inflammatory factors like macrophages and stimulate the secretion of IL-6 and IL-10 (Lira et al. 2011). The overconsumption of foods rich in calorie such as HFD, high-fructose diet, and sucrose-enriched diets has led to increased occurrence of metabolic disorders such as T2DM, obesity, NAFLD, CVD, etc. Also, when mimicked in in vivo models, high-sugar HFDs caused metabolic disorders like obesity, T2DM, metabolic cardiomyopathy, NAFLD, and atherosclerosis (Zhou et al. 2014). Interestingly, it was found that chronic low-grade inflammation was a common characteristic in all these metabolic disorders, which was associated with insulin resistance (Niu et al. 2016). High-fructose diet was also seen to exacerbate memory deficits in rodent models (Wu et al. 2015). Evidence suggests the role of advanced glycation end products (AGE) in development of AD by increasing the production of reactive oxygen species (ROS) (Chowdhury et al., 2018b). This finding has also been supported in in vivo studies; mice fed with AGE increased cognitive dysfunction and led to metabolic syndrome-like pathology (Cai et al., 2012a).

As previously mentioned, microglia-mediated inflammation is typically observed in AD brains, which plays an important role in the pathogenesis of AD. TNF-α is a pro-inflammatory cytokine that mediates Aβ-induced inflammation and the blockade of TNF-α receptor by infliximab, which is a TNF-α neutralizing drug, alleviates AβO-

induced impairment of neuronal signaling (Kim et al. 2016). The deleterious effect of serine phosphorylation of IRS-1, which leads to defective insulin signaling, is mediated by JNK (Bomfim et al. 2012). This same pathway is also implicated in the development of insulin resistance in adipocytes (Jiao et al. 2011). The downstream mediators of neuroinflammation include oxidative stress markers that increase the production of reactive oxygen and nitrogen species. These ROS damage nerve terminals and cause synaptic dysfunction inducing cognitive impairment (Agostinho et al. 2010). ROS destabilize macromolecules like lipids, proteins, and DNA and RNA by reacting with them leading to their dysfunction (Barone et al. 2014; Nunomura et al. 2012). Oxidative stress is observed in AD and other neurodegenerative disorders causing mitochondrial dysfunction therein (Bonda et al. 2014). Oxidative stress is also a common characteristic in metabolic syndrome. Metabolic syndrome is characterized by insulin resistance that is known to induce oxidative stress by dysregulating lipid and carbohydrate metabolism, inducing apoptotic signaling, activating GSK-3β pathway, and impairing mitochondrial function and energy balance (De La Monte and Tong 2014). The underlying pathology of obesity, a metabolic disorder, is associated with increased production of ROS, accelerated aging, oxidation, and inflammation (Ríos et al. 2014). Local inflammation is also observed in the adipose tissues in obesity with altered adipogenesis. Local inflammation in adipocytes leads to increased production and subsequent release of pro-inflammatory cytokines and adipokines like TNF-α, IL-1β, IL-18, IL-6, and leptin into the systemic circulation, which leads to the development of metabolic syndrome (Huffman and Barzilai 2009; Sutinen et al. 2012).

T2DM and other metabolic disorders share common metabolic mechanisms related to the hypothalamic dysfunction with AD. It was found that AβOs stimulate the production of ROS, eukaryotic translation initiation factor 2α phosphorylation (eIF2α-P), stimulate pro-inflammatory inhibitor of nuclear factor kappa-B (IKKβ)/nuclear factor kappa B (NFκB), and impairment in insulin signaling in a TNF-α dependent manner (Clarke et al. 2015). eIF2α is a translation initiation factor and eIF2α-P plays an important role in the post-transcriptional modification of β-secretase (BACE1) (Devi et al. 2012). These findings stress that inflammation is in fact a connecting trigger for insulin resistance development in both AD and T2DM. Mitochondrial dysfunction increases the risk of developing metabolic syndrome and AD. Indeed, neuroinflammation and mitochondrial dysfunction are associated with AD (Wilkins et al. 2014). Neuroinflammation leads to mitochondrial dysfunction, and the converse, mitochondrial dysfunction leads to neuroinflammation, is also true (Wilkins et al. 2014; Zhou et al. 2011).

Insulin signaling and metabolic dysfunction

Mitochondrial dysfunction is associated bioenergetic failure that can lead to progression of AD and other neurodegenerative disorders (Wilkins and Swerdlow 2016). Mitochondrial dysfunction results in energy imbalance, which is a common feature in aging-associated disorders like AD and metabolic disorders. Insulin is a metabolic hormone that controls glucose metabolism and appetite balance along with other peripheral signals such as leptin, adiponectin, cholecystokinin, and ghrelin (Cai et al., 2012b). Clinical evidence suggests that insulin influences glucose metabolism (Bingham et al. 2002). Energy regulation is impaired in metabolic syndrome and evidence suggests that calorie restriction prevents aging-associated neuronal damage and thus may be of importance in understanding the pathology of AD (Gillette-Guyonnet and Vellas 2008). Calorie restriction improves cognition by controlling neuroinflammation and ROS and improving synaptic plasticity. Indeed, dietary restrictions and exercise are associated with improved cognition in AD and overall improvement in metabolic syndrome, as discussed earlier. Energy requirement of brain is almost entirely governed by glucose metabolism, however, ketone bodies also play an important role as oxidizable substrates to provide energy for the brain (Lange et al. 2017). Moreover, in sufficient quantities, ketone bodies are reported to support the energy requirements and oxidative needs of neurons (Chowdhury et al. 2014). Energy deprivation is deleterious to neuronal viability and since glucose metabolism is impaired in AD. One of the clinical manifestations of AD is glucose hypometabolism in the temporal, posterior cingulate, prefrontal, and parietal cortex (Lange et al. 2017). Interestingly, glucose metabolism is significantly impaired in aged individuals carrying apolipoprotein E4 (ApoE4) allele (Reiman et al. 2004), which is a prime genetic factor for the development of sporadic AD (Jeong et al. 2019). Intriguingly, ApoE4 alterations are also manifested in metabolic disorders such as T2DM and hyperinsulinemia (Peila et al. 2002). Dysregulation in glucose metabolism pre-AD stage can be correlated with the development of insulin resistance in these individuals. Mitochondrial function also plays a vital role in AD pathogenesis. As such, mitochondria regulate glucose metabolism and interestingly, glucose hypometabolism is more pronounced in individuals with maternal history of AD, as mitochondrial DNA is inherited maternally (Mosconi et al. 2007). Mitochondrial enzymes also play an important role in the management of AD and metabolic syndrome. Decrease in silent information regulator 3 (SIRT3), a mitochondrial deacetylase enzyme, is observed in metabolic syndrome (Hirschey et al. 2011). Calorie-rich diet decreases SIRT3 levels, which is associated with the development of metabolic dysfunction (Hirschey et al. 2011). Recently, it was found that SIRT3 knockout mice when cross bred with APP/PS1 mice showed altered glucose metabolism, Aβ plaque formation,

and increased insulin resistance. Moreover, there was increased neuroinflammation as evidenced by elevated TNF-α, IL-1β, and COX-2 levels as well as increased microglial activity and expression (Tyagi et al. 2020). Further, insulin resistance worsens carbohydrate and lipid metabolism by increasing oxidative stress, GSK-3β activation, and dysregulating energy balance by impairing mitochondrial function (De La Monte et al. 2011). The term "type 3 diabetes" for AD can be attributed to the finding that the central nervous system (CNS) regulates peripheral glucose metabolism (Baeza-Raja et al. 2012) and metabolic dysfunction in CNS can increase the probability of developing obesity and insulin resistance (João et al. 2016; Meier and Nauck 2010; Thon et al. 2016).

As previously noted, hyperglycemia is a common characteristic of AD and other metabolic disorders like T2DM and is a marker to measure the extent of insulin resistance. Cognitive deficits in AD can directly be attributed to hyperglycemia. Admittedly, hyperglycemia increased mental subtraction errors in diabetic individuals in cognitive testing (Cox et al. 2005) and lower hemoglobin A1c levels correlated with low scores in neuropsychological testing (Cukierman-Yaffe et al. 2009). Moreover, increase in hemoglobin A1c levels is associated with increased risk of stroke, which may increase the risk of vascular dementia and dementia (Ramirez et al. 2015). Energy dysregulation and poor glycemic homeostasis can lead to a cascade of events leading to metabolic syndrome and AD. Hyperglycemia activates the polyol pathway and protein kinase c and increases the occurrence of AGE. These mechanisms lead to increased ROS production leading to altered brain function (Biessels et al. 2002; Brownlee 2005; Klein and Waxman 2003). Interestingly, energy metabolism of the brain is altered in 3xTg-AD and Tg2576 mice models showing insulin resistance suggesting that CNS metabolism may affect insulin signaling in the periphery (Velazquez et al. 2017). The role of insulin resistance in metabolic dysfunction is further highlighted in in vivo models of AD (Ruiz et al. 2016). Owing to these findings, it can be argued that AD is a metabolic disease with brain insulin resistance as the causative factor.

Recent evidence suggests that weight reduction may be beneficial in AD management as there is a common link between AD and obesity (Horie et al. 2016). High-sugar and HFDs show an increased propensity of developing cognitive impairment. In fact, diet-induced disruption of the blood brain barrier (BBB) establishes a correlation between obesity, dementia, and diet (Hsu and Kanoski 2014). Prolonged intake of HFD showed reduced expression of tight junction proteins in a rat model (Kanoski et al. 2010). In another study, HFD accelerated cognitive decline in AD by inducing Aβ 1–40 accumulation at the BBB as well as increasing the oxidative stress in cerebral vessels (Thériault et al. 2016). Obesity increases BBB permeability and along with insulin resistance elicit the breakdown of BBB. HFD-induced obesity and insulin resistance increased the permeability of low-molecular weight (fluorophore sodium fluorescein "NaFI") and high-molecular weight complex of Evans blue with albumin, with HFD-induced insulin resistance increasing the permeability of both NaFI and Evans blue-albumin complex (Yamamoto et al. 2019). This study further highlights the impact of insulin resistance and weight gain on BBB, which leads to cognitive decline and AD. Thus, there is a strong evidence linking obesity and metabolic dysregulation of lipid to the development of AD, which is caused by insulin resistance. Peripheral metabolic insulin and leptin regulate the expression of post-transcriptional regulators such as micro RNAs (miRNAs) that are implicated in the development and progression of metabolic syndrome and AD. In the next section we have discussed the involvement of miRNAs in these disorders and tried to highlight the importance of understanding the molecular mechanism governing miRNA involvement in these disorders.

miRNAs: Molecular link between metabolic syndrome and AD

Understanding the molecular mechanism behind the development of metabolic disorders and AD is necessary for the development of strategies that can delay the onset of these diseases or maintain them. miRNAs are important post-transcriptional regulators of protein coding genes that are involved in cell differentiation and survival. Thus, the deregulation of miRNAs is associated with the development of several pathologies including AD and T2DM. It is important to note that neuroinflammation plays a major role in the synthesis and regulation of miRNAs (Kawase-Koga et al. 2010) and miRNAs in turn are associated with inflammation and immunological responses (Dorval et al. 2013). Additionally, insulin and leptin hormones regulate several miRNAs expression in several brain regions, and clinically, metabolic syndrome-induced metabolic stress alters the expression of miRNAs related to AD (Codocedo et al. 2016).

P53 tumor suppressor protein corresponds to the transcription factor that regulates miRNA expression and it regulates the expression of stress response genes regulating miRNA expression. Additionally, p53 also regulates the expression of miR-34 and p53/miR-34 axis is upregulated in AD (Zovoilis et al. 2011). Thus, establishing that miRNAs are involved in either the regulation or the pathogenesis of AD. Intriguingly, p53/miR-34 axis is also upregulated in metabolic syndromes (Castro et al. 2013). Furthermore, miRNAs respond to dietary and lifestyle changes and risk factors of metabolic syndromes and AD are lifestyle dependent, such as poor diet and lack of exercise (Lukiw 2007; Mojtahedi et al. 2013; Smith et al. 2011). Thus, it can comfortably be argued

that AD and T2DM are not only linked at the pathological and cellular levels but also at the epigenetic level. Therefore, understanding the involvement of miRNA can contribute to newer therapeutic avenues for the prevention and more importantly for the diagnosis of AD.

Pathway involved in miRNA biogenesis

To understand the possible role of miRNAs and to establish a relationship between AD and metabolic syndrome, it is essential to appreciate its biogenesis pathway. miRNA biogenesis is almost entirely mediated by RNA polymerase II (pol II). RNA pol II synthesizes primary miRNA (pri-miRNA) transcripts, from certain precursor miRNA genes or post-transcriptional modifications (Dávalos et al. 2011). As a matter of fact, because miRNA's expression is governed exclusively by pol II, it is also regulated by epigenetic regulators and transcription factors associated with pol II. As discussed earlier, transcription factor that regulate miRNA expression also regulate p53 expression, which is associated with stress response. Pri-miRNA is processed to precursor miRNA (pre-miRNA) after sequential post-transcriptional modifications in the canonical pathway. This change is carried upon by Drosha microprocessor complex (DMC) inside the nucleus (Han et al. 2006). Exportin 5, which is an intracellular transporter, exports pre-miRNA into the cytoplasm (Okada et al. 2009). Inside the cytoplasm, Dicer cleaves the pre-miRNA and miRNA/miRNA* duplex is unwound by Argonuate (AGO) (MacRae et al. 2006). Evidently, fasting or obesity (and T2DM) regulate Dicer expression, thus increasing the processing of mature miRNAs (Schneeberger et al. 2013). Dicer deletion in the hypothalamus also causes insulin resistance, obesity, hyperlipidemia and altered pituitary-adrenal axis, leading to neuronal degeneration. When the miRNA complex is unbound by Dicer, two fragments viz. the mature strand and the complementary strand. The complementary strand is degraded and only the mature strand is utilized. These cleaved miRNAs are added to miRNA induced silencing complex (miRISC), which consists of Dicer, AGO, and a protein that recruits AGO to the miRNA-bound Dicer. When miRNAs bind to miRISC, it leads to the inhibition of translation and/or degradation of miRNA. Furthermore, metabolic alterations that regulate the autophagy process influence the stability of AGO and transcriptional repression of several miRNA targets (Martinez and Gregory 2013). This can consequently lead to metabolic syndromes and possibly AD. It is important to note that in an earlier study, conditional deletion of Dicer resulted in neurodegeneration and the induction of other metabolic diseases (Cuellar et al. 2008). Similarly, it was observed that in a brain-knockout Dicer model of mice, neuroinflammation, neurodegeneration, apoptosis, and tau hyperphosphorylation were enhanced greatly (Hébert et al. 2010). Thus, it can be summarized that any factor that has Dicer-dependent miRNA expression modulating activity, has the potential to affect pathological effects in T2DM- and AD-associated neurons. The details of miRNA biogenesis are illustrated in Fig. 3.

Altering the expression of different miRNA-induced silencing complex (miRISC) components also alters miRNA-mediated silencing without affecting the miRNA processing or expression. For example, in rat hippocampal neurons, AGO2 silencing is associated with an increase in APP, suggesting that APP translation is regulated by AGO2/miRNA pathway in rats (Vilardo et al. 2010). Presumably, miRNAs regulate many biological processes as evidenced by the up-regulated miR-34 expression in the liver of obese rats (Lee et al. 2010) and brains of aged mice with cognitive decline (Li et al. 2011). Moreover, silent information regulator (SIRT1) is also governed by miR-34a expression and is involved in neuroprotection, metabolic syndromes, ageing, and cancer (Codocedo et al. 2012). Taking these findings into account, an agonist of SIRT1 can possibly have a neuroprotective function. Indeed, in a neuroblastoma model induced by α-synuclein and Aβ (1–42) peptide, a SIRT1 agonist prevented neurodegenerative effects (Albani et al. 2009).

Role of miRNA in insulin signaling and AD

As discussed earlier, insulin resistance is the main highlight of all the metabolic syndromes. Co-expression of miR-124a and miR-375 regulates insulin exocytosis through the regulation of myotrophin protein, which is involved in vesicular fusion. miR-126 is a repressor of IRS-1 and, thus possibly involved in insulin signaling (Codocedo et al. 2016). miR-101-3p is involved in insulin signaling and lipid metabolism and is important for cell survival. It is present abundantly in pancreatic cells and are involved in downregulation of Bcl-2 leading to β-cell dysfunction (Zheng et al. 2015). Higher level of this miRNA is associated with T2DM (Higuchi et al. 2015; Santos et al. 2019). Furthermore, another study found that insulin resistance developed along with methionine choline-deficient diet downregulates miR-101-3p leading to liver injury with a potential of developing NAFLD (Meroni et al. 2019). Evidently, miR-101-3p precedes impairment in glucose metabolism as the levels are higher in patients with diabetes (Santos et al. 2019).

NFTs are formed by hyperphosphorylation of protein tau and deposition of misfolded Aβ plaques. Under normal circumstances, tau protein is present in the microtubule assembly and provides stability to it. However, when hyperphosphorylated, it is dissociated from the microtubule assembly affecting its stability. The balance between tau kinases and phosphatases is therefore crucial in the formation of NFTs. A growing body of evidence suggests the role of miRNAs in AD. Indeed, miR-101 is found to be strongly associated with AD; its downregulation increases APP levels and is found to be significantly reduced in AD cortex (Wang et al. 2011). Thus, miR-101 may significantly contribute to the development of AD. Furthermore, miR-9, miR-181, and

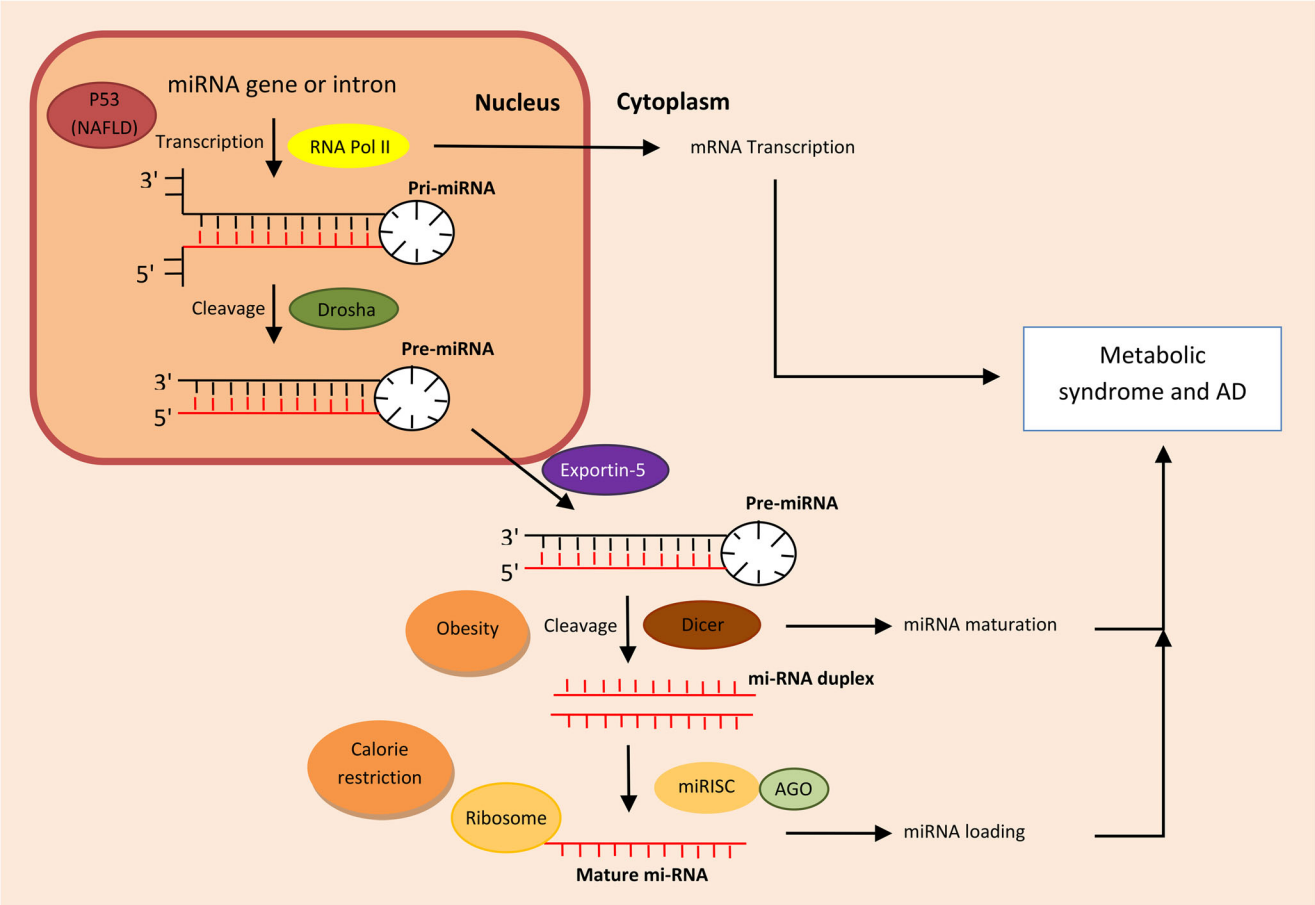

Fig. 3 miRNA biogenesis. miRNA biogenesis is almost entirely mediated by RNA Polymerase II (RNA Pol II). miRNA genes are converted to pri-miRNA by RNA Pol II-mediated transcription. These pri-miRNA transcripts are then acted upon by Drosha microprocessor complex forming pre-miRNA. Exportin-5 exports pre-miRNA out of the nucleus where it is cleaved by Dicer forming miRNA/miRNA* duplex. Argonuate (AGO) unwounds the miRNA duplex which is loaded into miRNA-induced silencing complex (miRISC). This leads to the formation of mature miRNAs. Dietary changes have a significant impact on the biogenesis of miRNAs regulating it at the transcription, Dicer expression, and miRNA loading levels.

miR-29 are also identified in AD brains further implying miRNA involvement in AD (Dorval et al. 2013). Another group has described the role of miR-26b in AD, which is involved in cyclin-dependent kinase 5 (Cdk5) transport (Liu et al. 2014). Predictably, it was found that miR-26b levels were higher in AD brains as Cdk5 is involved in the transcription of proteins that bring about tau hyperphosphorylation. Thus, it can be argued that miR-26b indirectly regulates tau hyperphosphorylation. Other groups have confirmed the involvement of miR-124 in AD, they found that its levels are increased in exercising brains (Mojtahedi et al. 2013), and its expression is downregulated in AD brains (Lukiw 2007). Another group has found that this miRNA downregulates BACE1 and, thus reduces Aβ levels (Fang et al. 2012), which further establishes the involvement of miRNAs in AD and metabolic syndromes. Interestingly, there are evidences suggesting that therapies for metabolic disorders like statins and metformin work at the miRNA level (Allen et al. 2012; Cufí et al. 2012).

Thus, in view of all these findings, it can be concluded that miRNAs act as a link between AD and metabolic syndromes, which may play a role in complex comorbidity between these two diseases; and can also be explored as biomarkers for the detection and diagnosis of both the metabolic syndromes. Similarly, miRNA can also provide the genetic understanding of both AD and T2DM and other metabolic disorders and can be explored to develop novel therapeutic targets. Especially with pharmacogenomics coming up to develop effective and safe medications, which is tailored to a person's genetic makeup, miRNA is an intriguing new target that can be further investigated to develop a targeted therapy for all the metabolic syndromes.

Gangliosides in insulin resistance and AD

Cell membrane microdomains are especially important in that they act as scaffolds for receptors to form intermediates with

other membrane elements. It is important that IR is present in its proper location in the membrane microdomains for insulin signal transduction. Signal transduction is dependent on the interactions of the IR with other membrane microdomain components like gangliosides (Kabayama et al. 2007). Gangliosides are formed from sphingolipids and are components of plasma membrane that regulate signal transduction. It is important to note that insulin resistance is a membrane microdomain disorder (Inokuchi 2010). Interestingly, ganglioside GM3 is known to regulate insulin resistance in diabetes. Moreover, TNF-α-induced insulin resistance is associated with GM3 upregulation, which leads to the loss of insulin receptors in the membrane microdomains (Kabayama et al. 2005). Indeed, GM3 synthesis was inhibited with a glucosylceramide synthase inhibitor, which improved TNF-α-induced insulin resistance (Sekimoto et al. 2012), and it also prevented phosphorylation of IRS-1 at the tyrosine residues (Tagami et al. 2002). Evidence suggests the positive role of GM3-synthase knockout mice in alleviating insulin signaling impairment (Yamashita et al. 2003). Caveolae are scaffolding proteins present on the plasma membranes of most cell types. Interestingly, a study suggests that the proper signaling of insulin is dependent on the association of IR with caveolin-1 (cav-1) for coupling of the receptor with IRS-1. Moreover, it was shown that GM3 upregulation dissociates IR-cav-1 interaction consequently leading to insulin resistance (Kabayama et al. 2007). Similarly, ganglioside GM1 is also associated with insulin resistance. Indeed, GM1 upregulation is linked to insulin resistance, which can be reversed by GM1 downregulation (Okabayashi et al. 2015).

Historical evidence suggests that gangliosides are also associated with AD pathogenesis showing Aβ interactions with different gangliosides (McLaurin et al. 1998). For example, AβOs support Aβ aggregation by binding to GM1, which leads to formation of toxic Aβ peptides (Hayashi et al. 2004). Intriguingly, ganglioside-associated Aβ (GAB) peptides have been discovered in postmortem AD brains (Hong et al. 2014). Parallelly, GM1 is found to be upregulated in AD brains and its binding to AβOs is leads to neurotoxicity, and unsurprisingly, GM1 blockade prevents LTP impairment by AβOs in mouse hippocampal neurons (Hong et al. 2014). GM1 gangliosides form a microdomain with cholesterol and sphingomyelin, which is associated with the toxicity of Aβ aggregates (Mori et al. 2012). Alteration in the membrane microdomain lipid composition leads to the accumulation of GM1, which causes increased AβO production through the formation of GAB complex (Yuyama and Yanagisawa 2009). GM2 is another ganglioside which is associated with AD. It was found that β-hexosaminidase, which is a GM2 degrading enzyme, decreased GAB levels improving cognition and anxiety in in AD mice (Knight et al. 2015). Surprisingly, accelerated developments of Aβ plaques and NFTs in diabetes are also associated with gangliosides. GAB is found to be increased exponentially in diabetic animal models. Supposedly, as the neuronal endocytic pathway is affected in diabetes, microdomain integrity is disturbed and the IR forms complexes with AβOs leading to deposition of Aβ plaques (Okabayashi et al. 2015). Moreover, it is studied that insulin treatment reduces GM1 levels leading to decreased Aβ deposition (Yamamoto et al. 2010).

Furthermore, GM3 metabolism is regulated by Aβ and APP. It was found that the binding of Aβ to GM3 significantly inhibited its metabolism (Grimm et al. 2012). As Aβ is associated with insulin resistance, it is highly probable that decrease in GM3 metabolism by APP and Aβ results in insulin resistance, which is further supported by an increase in GM3 levels in AD brains. As a matter of fact, blocking ganglioside synthesis by inhibiting glucosylceramide synthase alleviates insulin resistance, thus improving insulin signaling by preventing the dissociation IR (Herzer et al. 2016).In summary, ganglioside targeting and altering of GAB interaction can lead to potential therapeutic strategies for the management of both AD and T2DM associated with IR. A connection between ganglioside function and leptin signaling has also been implicated in the development of AD. Evidence suggests that GM3-related gangliosides influence leptin signaling (Inamori et al. 2018). The value of leptin signaling and its implication in AD and metabolic syndrome has further been discussed in the next section of the article.

Leptin hormone in AD and insulin resistance

For the management of insulin resistance and its associated conditions, a healthy lifestyle and a balanced diet is advised. As insulin resistance is the common hit between AD and metabolic syndrome, it is vital to understand strategies that may help to improve insulin sensitivity in these conditions. A recent clinical study highlights the importance of intermittent fasting for 14 h daily for 30 consecutive days suggesting that it has a positive effect on cognition, lipid and glucose metabolism, DNA repair, and metabolic syndrome (Mindikoglu et al. 2020). An important hormone involved in the hypothalamic control of food intake is leptin, which is an adipokine hormone involved in the regulation of adipose tissue mass and its metabolism for energy expenditure. Through its hypothalamic receptors, leptin control food intake by giving signals of satiety in a negative feedback manner by stimulating anorexigenic neuropeptides expression (Jéquier 2002). Thus, leptin has an obvious role in energy regulation and metabolism. Leptin receptors are found on the other brain regions besides hypothalamus, notably on the cerebral cortex and hippocampus. Interestingly, leptin receptor-deficient animals showed impaired spatial memory retention and LTP in the CA1 region of the hippocampus (Li et al. 2002). Thus, leptin receptors present in specific brain regions highlight their potential

functions in various brain regions. Evidently, leptin is involved in neurogenesis, synaptogenesis, axon growth, and dendritic morphology (Morrison 2009). Increased in leptin levels is associated with improved insulin signaling. Leptin replacement in a leptin-deficient individual showed improved insulin sensitivity globally (Frank-Podlech et al. 2018). Remarkably, leptin decreases hepatic and systemic triglyceride levels, which is independent of its satiety effect (Brown et al. 2018). Moreover, leptin resistance is observed in obese adults having cognitive impairment (Smith et al. 2019).

PTP1B is known to play a key role in regulation of insulin signaling. PTP1B is a negative regulator of leptin signaling leading to impaired cognition, which has been seen in AD brains (Smith et al. 2019). The presence of leptin receptors in the hippocampus and cerebral cortex is of great importance as leptin signaling in these brain regions is essential for memory and cognition (Winocur et al. 2005). Evidently, leptin provides protection against both Aβ and tau hyperphosphorylation, which are the pathological hallmarks of AD (Greco et al. 2009). Intriguingly, leptin decreases BACE1 activity by altering lipid composition of the membrane lipid rafts (Greco et al. 2009). Metformin, the drug of choice for the management of insulin resistance, acts by decreasing hyperphosphorylated tau levels and phosphorylated JNK levels in obese, leptin-resistant mice (Li et al. 2012).

In obesity, similar to insulin resistance in T2DM, a sensitive resistance to leptin occurs resulting in an inability to detect satiety despite high energy levels (Arnoldussen et al. 2014). There is lower brain leptin level because of leptin resistance in obesity. This is due to impaired transport of leptin from the periphery to brain. As mentioned earlier, miRNAs are involved in AD and metabolic syndromes. Interestingly, leptin is known to regulate miRNA expression in various brain regions and plays a vital role in the alteration of metabolic stress in metabolic syndrome. The most common miRNA that is downregulated in obesity is miR-26b because of high peripheral leptin levels (Xu et al. 2013). Reduction in central leptin levels by cholesterol administration results in the deregulation of miR-125b, miR-98, miR-30, miR-107, which are reportedly altered in AD brains (Liu et al. 2014). Moreover, miR-132 levels are 60% lesser in leptin-deficient mice as compared to the wild type. miR-132 is important for cognition, memory, maintaining LTP, and neuronal growth and administration of leptin lead to increase in the levels of this miRNA (Dhar et al. 2014). Low level of leptin causes AD and leptin resistance is observed in LOAD (Lau et al. 2013). Leptin supplementation is associated with neuronal development, which further supports the fact that leptin helps in proper neuronal functioning (Bouret 2010). Leptin impairment can also be caused by HFD, which again is associated with AD.

In conclusion, proper hippocampal signaling of leptin and insulin is necessary to maintain a balance between both AD and T2DM.

Conclusion

To summarize, the review refers to some of the key cellular and molecular mechanisms that are implicated in AD and metabolic disorders, and how neurons become resistant to insulin in AD, which ultimately leads to synaptic and memory impairments. Different targets that are now being studied for AD also are known to influence T2DM. For instance, thiazolidinediones and GLP1/GIP agonists are already under clinical trials for its use in AD. Anti-obesity drugs have also been found to have an effect in Alzheimer's and that AD and metabolic syndrome are in fact linked and highly dependent on diet. HFD results in inflammation and also insulin resistance in few cases. Identification of other molecular and genetic mechanisms of the formation of Aβ and its degradation as well as other pathogenic factors of AD and diabetes, may provide novel potential targets for disease modifying therapies in AD. Furthermore, development of novel strategies for identification of early onset of the disease will likely increase the efficacy of both anti-diabetic and anti-Alzheimer's therapies and maintain the condition before neuronal functions are severely affected in AD brains.

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