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Is Alzheimer's disease related to metabolic syndrome? A Wnt signaling conundrum

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia, affecting more than 36 million people worldwide. AD is characterized by a progressive loss of cognitive functions. For years, it has been thought that age is the main risk factor for AD. Recent studies suggest that life style factors, including nutritional behaviors, play a critical role in the onset of dementia. Evidence about the relationship between nutritional behavior and AD includes the role of conditions such as obesity, hypertension, dyslipidemia and elevated glucose levels. The coexistence of some of these cardio-metabolic risk factors is generally known as metabolic syndrome (MS). Some clinical studies support the role of MS in the onset of AD. However, the cross-talk between the molecular signaling implicated in these disorders is unknown. In the present review, we focus on the molecular correlates that support the relationship between MS and the onset of AD. We also discuss relevant issues such as the role of leptin, insulin and renin–angiotensin signaling in the brain and the possible role of Wnt signaling in both MS and AD. We discuss the evidence supporting the use of *ob*/*ob* mice, high-fructose diets, aortic coarctation-induced hypertension and *Octodon degus*, which spontaneously develops β-amyloid deposits and metabolic derangements, as suitable animal models to address the relationships between MS and AD. Finally, we examine emergent data supporting the role of Wnt signaling in the modulation of AD and MS, implicating this pathway as a therapeutic target in both conditions.

Abbreviations: AMPK, AMP-activated protein kinase; STAT, activator of transcription; AGE, advanced glycation end products; AD, Alzheimer's disease; APP, amyloid precursor protein; Aβ, amyloid-β peptide; ACE, angiotensin converting enzyme; Ang I, angiotensin I; AR-II, angiotensin II receptors; Ang II, angiotensin II; ApoJ, apolipoprotein J; ASCVD, atherosclerotic cardiovascular disease; ABCA7, ATP-binding cassette A7; BP, blood pressure; BBB, blood–brain barrier; BMI, body mass index; BMP-4, bone morphogenetic protein 4; C/EBPα, CCAAT/enhancer binding protein α; CNS, central nervous system; CSF, cerebral spinal fluid; DAG, diacylglycerol; Dkk1, Dickkopf 1; Dvl, disheveled; Erk1/2, extracellular-signal-regulated kinases; Fz2, frizzled 2 receptor; Fzd, frizzled; GSK-3β, glycogen synthase kinase-3β; HDL, high-density lipoprotein; GLP-1/GIP-1, incretins; IRS-1, insulin receptor substrate-1; IR, insulin receptor; IDE, insulin-degrading enzyme; IL-18, interleukin-18; IL-1β, interleukin-1β; JAK, Janus kinase signal transducer; JGA, juxtaglomerular apparatus; LRb, leptin receptor; LRP, lipoprotein receptor-related protein; LTP, long-term potentiation; LDL, low-density lipoprotein; LEF, lymphoid enhancer-binding factor; MS, metabolic syndrome; NFTs, neurofibrillary tangles; PPARγ, peroxisome proliferator-activated receptors γ; PI3K, phosphatidylinositide 3-kinases; PLC, phospholipase C; PCP, planar cell polarity pathways; PKA, protein kinase A; ROS, reactive oxygen species; RAS, renin–angiotensin system; sFRP1, secreted frizzled-related protein 1; SORL1, sortilin-receptor; TCF, T cell specific transcription factor; TAC, tranverse aortic coarctation; TNF-α, tumor necrosis factor-α; T2DM, type 2 diabetes mellitus.

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Contents

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia associated with age, affecting approximately 36 million people worldwide. Moreover, it is estimated that by 2050, the number of cases will rise to 110 million (Hampel et al., 2011; Wimo et al., 2013). Therefore, AD represents a critical health problem worldwide (Ballard et al., 2011; Mayeux and Stern, 2012). From a cellular perspective, AD is associated with aberrant protein processing and is characterized by the presence of extracellular aggregates of amyloid-β peptide (Aβ) called senile plaques and by intracellular clusters of hyper-phosphorylated *tau* protein called neurofibrillary tangles (NFTs) (Fig. 1) (Selkoe et al., 2012; Serrano-Pozo et al., 2011). Clinically, AD is characterized by a progressive loss of cognitive abilities, of which the most affected are memory and learning (Ballard et al., 2011; Castellani et al., 2010; LaFerla et al., 2007). Evidence indicates that synapses are particularly vulnerable to AD. In fact, the loss of synapses and dendritic spines correlates better with cognitive decline in AD than does the loss of neurons (Benilova et al., 2012; Cerpa et al., 2008; Li et al., 2011b).

While no cure exists for AD and the molecular mechanisms that trigger the disease are not fully understood, several studies have suggested diverse mechanisms to explain the onset of AD, including the genetic burden passed from parents, which could playa major role in determining the onset of AD. In fact, mutations that either cause or increase the risk of AD could be responsible for neuronal degeneration and cognitive dysfunction. Although the majority of AD cases are sporadic, molecular genetic analyses suggest that there are likely to be many genes that influence susceptibility to AD (Levy-Lahad et al., 1995; Piaceri et al., 2013; Sherrington et al., 1995). In addition, increased oxidative stress (uncontrolled production of highly reactive oxygen species [ROS]) and impaired cellular energy have been postulated as risk factors for the onset of AD. Of note, in the brain of patients with AD, increased levels of oxidatively modified proteins and lipids have been reported. The generation of ROS has been linked to failures in the metabolism of some metals, including Fe^{2+} and Cu^{+} (Bush et al., 2003; Cai et al., 2011; Cerpa et al., 2005; Miranda et al., 2000; Smith et al., 1997). Further, disturbances in cellular energy homeostasis, including the deregulation of glucose metabolism, increase neuronal dysfunction and lead to a loss of synaptic networks and a decreased rate of Aβ clearance (Bosco et al., 2011; Burns et al., 2013; Cunnane et al., 2011; Gabuzda et al., 1994; Kapogiannis and Mattson, 2011; Zolezzi and Inestrosa, 2014). Additionally, altered proteolytic processing of the amyloid precursor protein (APP) increases the production and accumulation of neurotoxic Aβ in the brain. The latter supports the so-called "amyloid hypothesis", which implicates Aβ as the pathological initiator of both familial and sporadic AD (Hardy, 1997; Selkoe, 2000; Tandon et al., 2000; Van Gassen and Annaert, 2003). The deregulation of Ca^{2+} has also been associated with the onset of AD because changes in Ca^{2+} lead to the dysfunction and death of neurons (Mattson et al., 1993; Supnet and Bezprozvanny, 2010). Another factor that could lead to the onset of AD includes the deregulation of glial cell activity. Both astrocytes and microglia are critical to several brain functions (Fig. 2), including glutamate transmission, inflammatory signals, redox imbalance and glucose and insulin metabolism. The failure of these glial functions could lead to neuronal death and stimulate the accumulation of Aβ and *tau* aggregates at the onset of AD (Clarke and Barres, 2013; Dumont and Beal, 2011; Li et al., 2011a; Tan et al., 2012).

Finally, in recent years, some clinical studies have proposed that nutritional behavior could be an important factor in the progression of AD. In fact, calorie restriction, Mediterranean diet and drinking red wine rich in polyphenols have been reported to attenuate AD deterioration of spatial memory, delay the onset of dementia and reduce amyloid neuropathology (Bucht and Sandman, 1990; Kamphuis and Scheltens, 2010; Wang et al., 2005, 2014a). On the other hand, some epidemiological studies also suggest a relationship between Metabolic Syndrome (MS) and AD (Razay et al., 2007; Vanhanen et al., 2006) which links unhealthy nutritional behavior and its associated diseases such as obesity, hypertension and type 2 diabetes mellitus (T2DM) (Gomez-Pinilla, 2008) with the onset of dementia syndromes, including AD (Gardener et al., 2012; Roberts et al., 2014; Vemuri et al., 2012). MS refers to a cluster of cardiometabolic risk factors (obesity, insulin resistance, hypertension, and dyslipidemia) unequivocally linked to an increased risk of developing atherosclerotic cardiovascular disease (ASCVD) and T2DM. Although the concept of a "syndrome" has been debated, MS is clinically useful for identifying people who are at risk of these complications, although it remains unclear whether the syndrome as a whole confers more risk than the sum of its parts. Different definitions of MS have been published (Huang, 2009). The most widely used are the updated criteria published by the American Heart Association and the National Lung and Blood Institute in 2005 (Grundy et al., 2005) (Table 1).

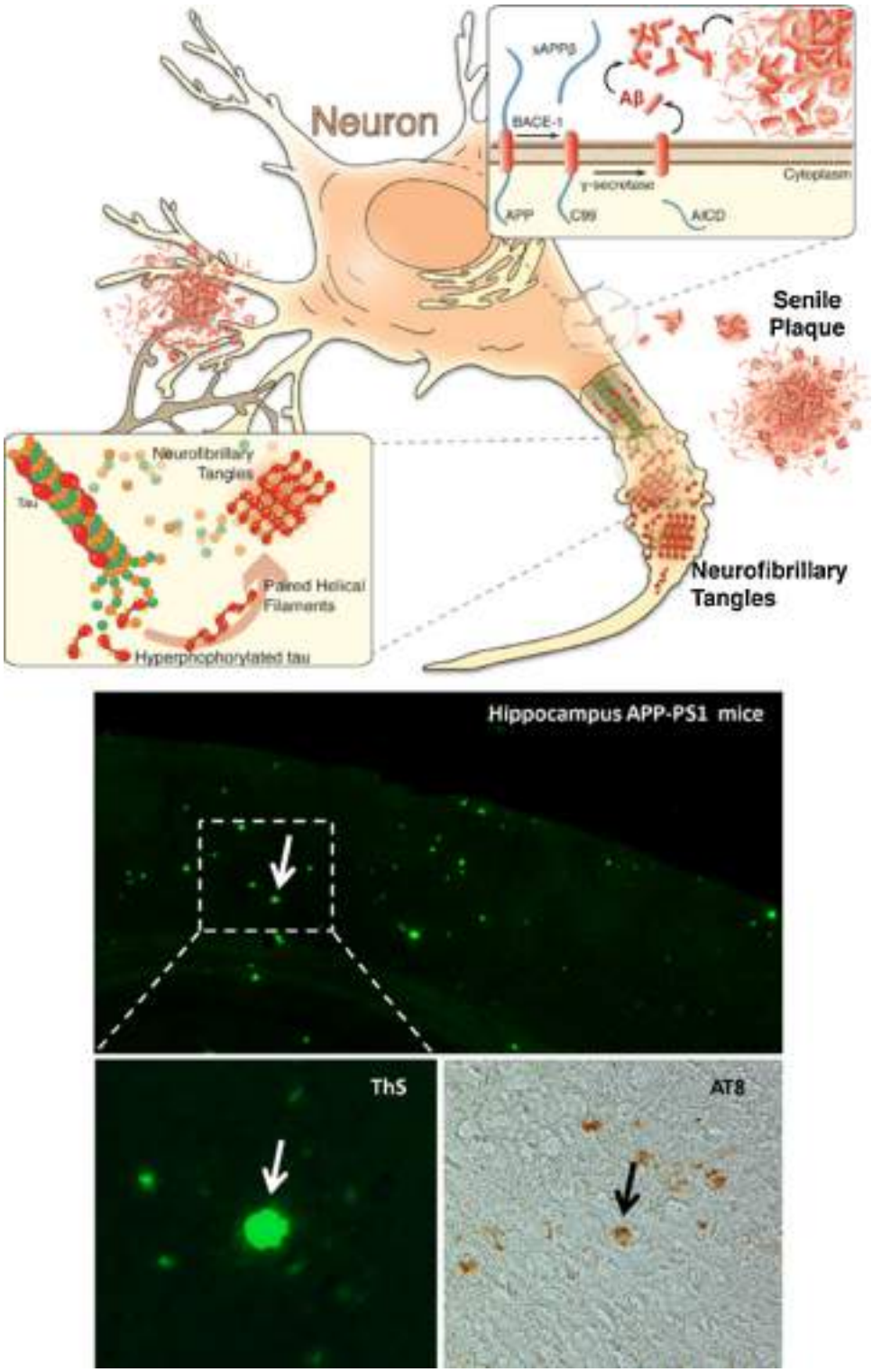

Fig. 1. Classical view of the main pathological events in AD. (A) The scheme shows a neuron with the two main neuropathological hallmarks of AD. On the right, above insert, senile plaque formation in the extracellular space is shown from the amyloidogenic processing of APP. On the left, below insert, NFT formation in the parenquimal space is shown from aberrant processing of *tau* hyperphosphorylation. These two protein aggregates are responsible for synaptic failure and neuronal damage. **sAPPβ**: soluble peptide APPβ; **BACE-1**: β-site amyloid precursor protein cleaving enzyme 1; **C99**: cleavage of the membrane-anchored C-terminal stump of APP 99; **AICD**: APP intracellular domain. (B) This picture shows the brain of a double transgenic mouse (APP/PS1) stained with thioflavin-S showing senile plaques (white arrow) and immunostaining with the AT8 antibody showing staining of *tau* protein (black arrow).

MS currently has a worldwide prevalence of 23% (Ceriello and Colagiuri, 2008), and the annual expenditure generated by this syndrome is between U.S. $ 5000 and U.S. $ 8000 per person (Boudreau et al., 2009). Over the last few years, several reports have linked MS to an increased risk of cognitive decline associated with age (Ho et al., 2008). Similarly, other studies have suggested that having MS increases the risk of vascular dementia and AD (Solfrizzi et al., 2010; Watts et al., 2013). More recent studies using

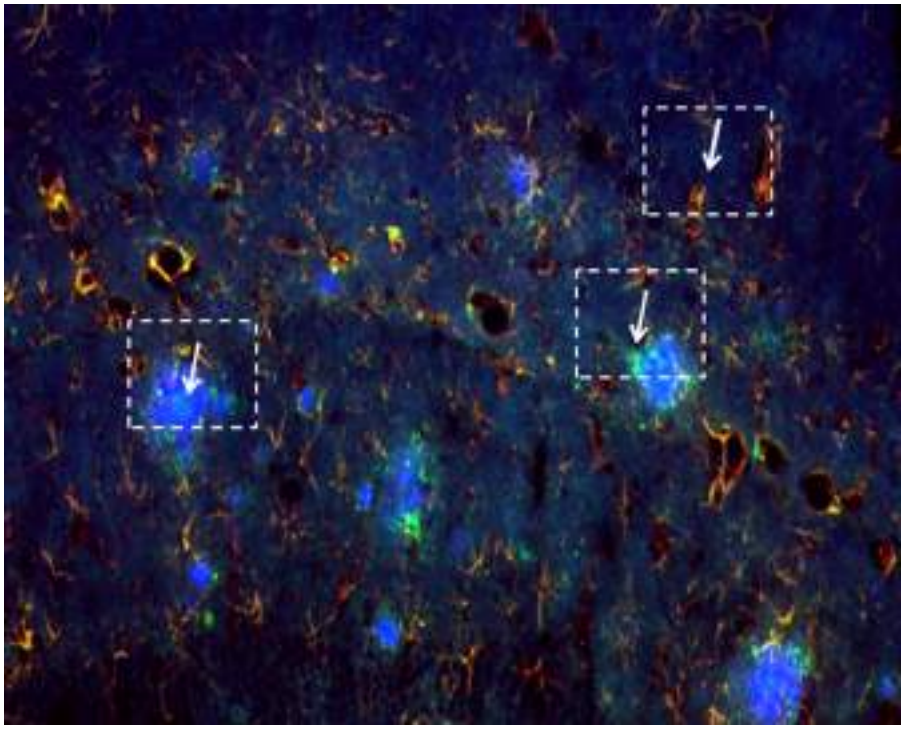

Fig. 2. Response of glial cells in AD brain. This picture shows the cortex of a transgenic mouse (APP/PS1) with triple immunostaining, a glia cell marker (GFAP antibody, in red, white arrow), a microglial marker (CD11b antibody, in green, white arrow) and X-34 stain to show senile plaques (blue, white arrow) were used. The staining highlights the role of astrocytes and microglia around each senile plaque that contributes by releasing proinflammatory cytokines and adipokines in AD.

Table 1
Clinical parameters used in the diagnosis of MS.

Parameters	Values
Abdominal obesity	>102 cm (men) and 88 cm (women)
HDL	HDL <40 mg/dl (men) and <50 mg/dl (women)
Triglycerides	≥150 mg/dl
Blood pressure	≥130/85 mmHg
Fasting glucose	≥100 mg/dl

According to the adult treatment panel-III (*ATP-III*).

an animal model of MS that involves feeding mice a high-fructose diet showed an increase in insulin levels, triglycerides and the insulin resistance index, as well as the deregulation of energy metabolism and loss of memory. This model of MS links glucose intake with failures in the brain and reports a critical role for insulin in the brain. Indeed, further studies are necessary to fully understand the relationship between MS and cognitive deficits (Agrawal and Gomez-Pinilla, 2012; de la Monte and Tong, 2013; Sharma et al., 2012; Yates et al., 2012). However, given the enormous volume of information that already exists about the related pathogenic mechanisms of MS and AD (Calvo-Ochoa and Arias, 2014; Duron and Hanon, 2008a,b; Farooqui et al., 2012; Misiak et al., 2012), it seems timely to review the current evidence and provide a perspective of current research questions and unmet research needs.

The present review aims to summarize the available data connecting AD with the four pillars of the MS diagnosis (visceral fat deposition; atherogenic mixed dyslipidemia; hypertension; and deregulation of glucose homeostasis). Finally, we review the available data, including our own findings, supporting a role for the Wnt signaling pathway in both MS and AD, thus providing a novel link between the entities that is potentially amenable for therapeutic modulation.

2. Obesity and AD

More than 70 years ago, a seminal study by the renowned biochemist and gerontologist Clive McCay established that excess calorie intake decreases survival in mice (McDonald and Ramsey, 2010). The life expectancy of obese individuals with a body mass index (BMI) >40 is reduced by 6–12 years (Fontaine et al., 2003). In this sense, obesity, a key risk factor of MS, has become a worldwide public health problem of epidemic proportions, with approximately 500 million obese adults worldwide (Businaro et al., 2012). Several epidemiological studies have suggested that being overweight or obese increases the risk of AD and dementia (Anstey et al., 2011; Jauch-Chara and Oltmanns, 2014; Kivipelto et al., 2005; Whitmer et al., 2007; Xu et al., 2011). In addition, a link between obesity-related complications and AD has been identified by epidemiological research, involving bariatric interventions like a novel therapy for AD (Ashrafian et al., 2013). Some studies suggest an association between T2DM and fatty liver disease (NAFLD), the hepatic manifestation of MS (Tarantino and Finelli, 2013), with AD (de la Monte et al., 2009) (see Section 5 of this review for details). Patients with T2DM have twice the incidence of sporadic AD than do their non-diabetic counterparts (Kravitz et al., 2013; Vignini et al., 2013). NAFLD is used to describe a clinicopathological entity that is characterized by hepatic triglyceride accumulation in the absence of excessive alcohol intake that may progress to cirrhosis but is also associated with increased risks of cardiovascular events and T2DM development (Anstee and Day, 2013; Anstee et al., 2013). Reports show that up to 50% of NAFLD patients may experience mild cognitive impairment (Newton, 2010). NAFLD pathophysiology is complex, but insulin resistance has a central role in its development and is therefore closely linked to MS and T2DM (Arrese, 2010; Von Bernhardi et al., 2010). The underlying mechanisms of the association among obesity, T2DM, NAFLD and AD are not precisely defined, but some mechanistic

insight can be inferred. For example, obesity has been associated with several processes related to the acceleration of aging, including the excessive production of free radicals, oxidation and inflammation (Bhat, 2010; Dandona et al., 2005; Haffner, 2006; Miranda et al., 2000). Additionally, interesting studies in *Rhesus* monkeys with increased BMI due to a high fat diet have shown up-regulated neuronal death genes (Mitchell et al., 2012). Experimentally induced T2DM and NAFLD in rodents are associated with the impairment of spatial learning and neurodegeneration (de la Monte et al., 2009), lending support to the connection between disturbed insulin homeostasis and AD.

Additional insights into the links between obesity, insulin-resistance states and AD can be obtained from the altered adipose tissue physiology in these conditions. Obesity is associated with hyperplasia and hypertrophy of adipose tissue and with altered adipogenesis and local inflammation. This can lead to the subsequent release of several cytokines and adipokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-18 (IL-18) and leptin, into the systemic circulation, modulating the function of several organs and leading to the pathogenesis of MS (Huffman and Barzilai, 2009; Sutinen et al., 2012). Among the adipose tissue-derived factors collectively termed adipokines, leptin is one of the best characterized. Leptin regulates various physiological processes including appetite control, body weight, neuroendocrine functions and glycaemia (Coppari and Bjorbaek, 2012). Moreover, the actions of leptin affect several tissues and could play a critical role in the onset of AD and MS. In fact, epidemiological studies have unequivocally implicated decreased leptin levels in the pathogenesis of AD. Clinical studies indicate that higher circulating levels of leptin are associated with a reduction in AD incidence. In fact, regulating the levels of leptin has been proposed as a therapeutic approach to control the onset of MS (Dalamaga et al., 2013; Fewlass et al., 2004; Lieb et al., 2009). In studies using mice that lack leptin (*ob*/*ob* mice) (Ingalls et al., 1950), the complex phenotype involves pathology in almost all organs, which is most likely explained by compensatory mechanisms in response to the lack of leptin leading to multiple secondary effects (Schwartz and Baskin, 2013).

In the brain, the interaction of leptin with the leptin receptor (LRb) leads to the activation of several intracellular pathways including the Janus kinase-signal transducer and activator of transcription (JAK-STAT), extracellular-signal-regulated kinases (Erk1/2), 5′ AMP-activated protein kinase (AMPK) and phosphatidylinositol 3-kinase (PI3K) pathways (Schwartz and Baskin, 2013). The activation of leptin signaling in the brain leads to several critical processes that are necessary for neuronal life span (SIRT1 activation and autophagy). Each of these processes is decreased in AD (Godoy et al., 2014a,b), including the stimulation of dendritic growth in hippocampal and cortical neurons *in vitro*, adult hippocampal neurogenesis, enhanced hippocampal long-term potentiation (LTP) through enhanced NMDA receptor function and regulation of feeding behavior *in vivo* (Fig. 3A). *Ob*/*ob* mice present failures in hippocampal activity associated with learning functions. In summary, the activation of leptin signaling plays a critical role in brain function and most likely delays the development of AD (Garza et al., 2008; O'Malley et al., 2007; Stranahan et al., 2008a; Valerio et al., 2006).

2.1. Child obesity; early impacts on the CNS

Currently, MS affects not only adults but also to 4–8% of adolescents and children; this percentage increases to approximately 30% in obese children (Arnaiz et al., 2010; Barja et al., 2003a,b; Cook et al., 2003; Mardones et al., 2013; Weiss et al.,

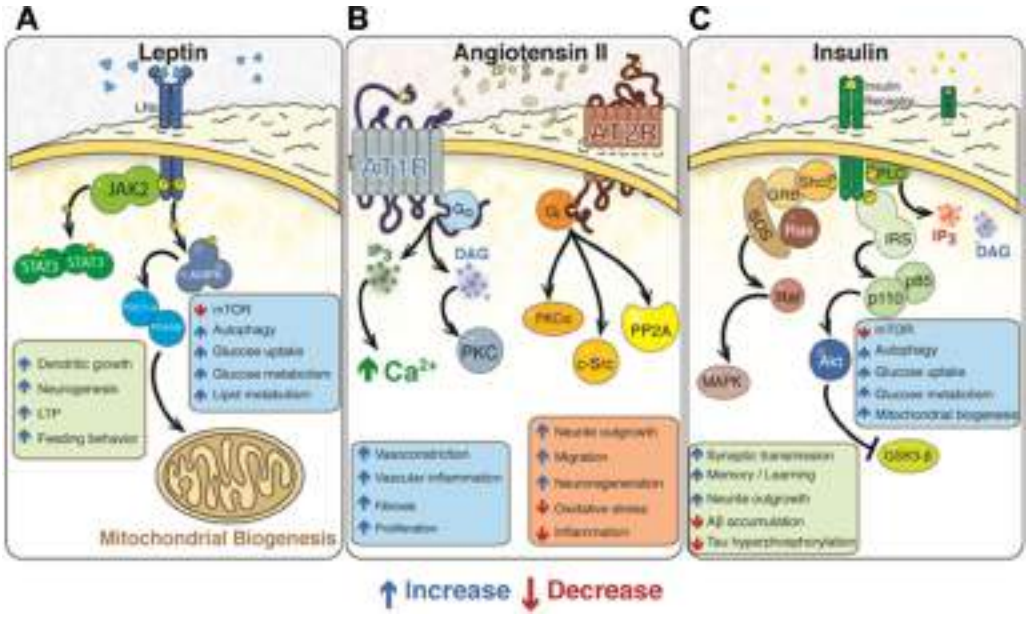

Fig. 3. (A) The main signaling pathways of leptin in the brain. Binding of leptin to the leptin receptor (LepR) stimulates tyrosine kinase activity and activates two cascades; the JAK/STAT and AMPK pathways. The JAK/STAT cascade carries out gene expression that stimulates CNS processing and feeding behavior (left below insert), this pathway promotes dendritic outgrowth, neurogenesis and LTP. The AMPK cascade leads to PCG1-α activation and mTOR inhibition. The latter pathway stimulates cellular energy metabolism processing in neurons: autophagy, glucose uptake and lipid metabolism (right above insert). (B) The main signaling pathways of angiotensin-II in the brain. Binding of angiotensin-II to the angiotensin-II receptor (AR) type 1 (AT1) and type 2 (AT2). AT2 stimulates G protein coupled activity while AT1 stimulates Gα subtype leading to activation of PKC and the rise of intracellular Ca^{2+} levels. This pathway promotes the canonical effects of the renin–angiotensin system (RAS) including vasoconstriction, vascular inflammation, fibrosis and proliferation. On the other hand, AT2 activation, stimulates Gi subtypes leading to activation PKCα, c-Src and PP2A. This pathway promotes the non-canonical effects of angiotensin-II including neurite outgrowth, migration, neuroregeneration and decreased inflammation and oxidative stress. c-Src, proto-oncogene c-Src; PP2A, Protein phosphatase 2. (C) The main signaling pathways of insulin in the brain. Binding of insulin to the insulin receptor (IR) stimulates tyrosine kinase activity and activates two cascades; MAP kinase (MAPK) and insulin receptor substrate (IRS) dependent pathways. The IRS cascade carries out Akt activation stimulating cellular energy metabolism processing: mTOR inhibition, increased autophagy and glucose uptake (right insert). The MAPK dependent pathway stimulates CNS processing and neuroprotection (synaptic transmission, memory, learning and decreased Aβ accumulation and *tau* hyperphosphorylation) (left below insert).

2004). MS affects the brain and cognition in all stages of life (Yates et al., 2012). Studies show that obesity in children is associated with cognitive compromise, mainly in executive functioning (Lokken et al., 2009). For example, a comparison between healthy and obese children showed a considerably reduced amount of brain activation to food in the bilateral prefrontal cortex, a region implicated in cognitive control (Bruce et al., 2013). In addition, more social-behavioral skills were noted for overweight girls, indicating that a change in overweight status during the early school years is a significant risk factor for poor academic performance and behavior in girls but not in boys (Datar and Sturm, 2006). In fact, high adolescent BMI has a strong association with neuro-structural deficits, which is evident in the orbitofrontal cortices and reflected behaviorally in the inferior development of executive function (Reinert et al., 2013). MS impacts the brain by producing elevated blood pressure, which is more frequent in overweight or obese children; those with systolic blood pressure $\geq$90th percentile for their age had significant impairments in attention, visual-spatial and math performance (Lande et al., 2003). Adolescents with T2DM present with cognitive impairment, a reduction in frontal lobe volumes and white matter microstructural integrity problems (Yau et al., 2010). Brain imaging demonstrated that obese adolescents with T2DM had smaller hippocampal volumes and more frontal lobe atrophy (Bruehl et al., 2011; Convit, 2012). Additionally, compared with well-matched lean subjects, obese adolescents have specific gray matter volume deficits in the orbitofrontal cortex, which are associated with uninhibited feeding behavior. Insulin resistance in obese children may contribute to decreased executive function and structural deficits, a mechanism previously demonstrated in adults (Maayan et al., 2011). A study on 120 children and adolescents between 6 and 18 years of age submitted to magnetic resonance imaging (MRI) suggested that obesity is associated with a decreased volume of frontal and limbic cerebral gray matter regions (Alosco et al., 2013). However, another study observed that overweight adolescents showed increased gray matter volume in the right hippocampus (Moreno-Lopez et al., 2012). Authors have documented diminished cognitive skills and reductions in brain structural integrity among adolescents with MS, thus suggesting that even relatively short-term impairments in metabolism without clinically manifest endothelial-vascular disease can have an important effect on cognitive development (Yau et al., 2012). This evidence reinforces the idea that childhood obesity has an early impact on the brain, possibly through a direct molecular mechanism. Possible major contributors include an excessive production of adipokines from visceral abdominal fat, an inappropriate activation of signaling pathways before the onset of cerebrovascular disease or independent vascular factors. In contrast, cross-sectional studies have not demonstrated that obesity contributes to a decline in intelligence quotient (IQ), even among obese individuals who displayed evidence of MS and elevated systemic inflammation (Barja et al., 2009; Belsky et al., 2013).

Studies in a population-based sample of 598 adolescents found genetic variations in fat mass and obesity (FTO) associated genes in a well-replicated gene locus associated with obesity and possibly with reduced regional brain volumes in the elderly (Melka et al., 2013). In recent genome-wide association studies (GWAS), researchers identified a single nucleotide polymorphism (rs2241423) within the last intron of MAP2K5 that was associated with a higher BMI. MAP2K5 is an element of the MAPK-family intracellular signaling pathways, which respond to extracellular central nervous system (CNS) modulators such as the brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF); both are neurotrophins with important roles in feeding behavior, food intake regulation, energy metabolism and weight control. In a study of two cohorts of children from Sweden and Greece, an association between variants in these genes (BDNF and NGF) and rs2241423 with BMI and obesity was demonstrated (Rask-Andersen et al., 2012). Other studies show a possible disturbance of biomarkers in the brain associated with obesity in children, including plasma BDNF, which is lower in obese prepubertal children than in lean controls (Corripio et al., 2012; Roth et al., 2013). Recent studies on BDNF found an association between the polymorphism Val66Met and obesity in 300 healthy children (Skledar et al., 2012). Additionally, retinal arteriolar interior diameter may serve as a possible noninvasive proxy for brain atrophy in obese adolescents (Tirsi et al., 2013). In juvenile mouse studies, exposure to a high fat diet (HFD) is associated with poor performance in spatial learning, impaired relational memory and a reduction in hippocampal neurogenesis. For that reason, research investigating how saturated fat consumption in adolescence can affect cognitive skills is of great interest (Boitard et al., 2012).

2.2. Maternal obesity; impact on the fetal brain

The prevalence of maternal obesity has risen considerably in recent years, with approximately one in five pregnant women in the United Kingdom (UK) now classed as obese (BMI $\geq$ 30) (O'Reilly and Reynolds, 2013). Obesity during pregnancy results in an increase in metabolic disorders for the mother and the child. Maternal metabolic disturbances can have a strong impact on the uterine micro-environment, possibly increasing later risks of metabolic disease in childhood and adolescence (de Boo and Harding, 2006; Power and Schulkin, 2012). The fetal brain is a major target for systemic inflammation secondary to maternal obesity. For example, leptin is secreted by the placenta into both the maternal and fetal bloodstreams, and obese pregnant women have higher circulating leptin levels that could theoretically benefit brain development. However, there is a decrease in the expression of the leptin receptor in the placenta of obese women (Farley et al., 2010). Interestingly, maternal obesity induced by a HFD in mice results in the diminished migration and maturation of stem-like cells in the 3rd ventricular region and in the cortex (Stachowiak et al., 2013b). A similar study using RNA analysis (GeneChip) showed deep dysregulation in expression clusters of genes that could contribute to the transfer of the maternal phenotype (Stachowiak et al., 2013a). Other poor outcomes associated with maternal obesity are early embryonic loss, fetal growth retardation and brain developmental abnormalities, including the abnormal development of both the ventricles and the choroid plexus (Luzzo et al., 2012). In studies feeding a HFD to pregnant rats, the proliferation of neural progenitors was increased in the neuroepithelium of the hippocampus and cortex in fetuses from mothers fed the HDF compared with controls but decreased within the dentate gyrus (DG). In the same study, apoptosis in the hippocampus was increased and calretinin-positive neurons in the DG were decreased (Niculescu and Lupu, 2009). Other authors reported that pregnancy and obesity induced by a HFD or highly palatable food specifically impairs reversal learning, a type of adaptive behavior, while leaving plasma metabolic parameters intact in the offspring of rats, suggesting early functional and structural damage. In offspring born in an adverse intrauterine nutritional context, damage may occur to the CNS rather than to the metabolic system (Wu et al., 2013). Tessier-Lavigne and coworkers proposed a link between abnormal prenatal developmental processes and AD. Prenatal pruning is mediated by another portion of APP, called the amino-terminal fragment of APP (N-APP), which causes a cascade of events that results in the loss of unneeded neurons (Nicholson, 2009; Nikolaev et al., 2009). Recent studies on pregnant APP/PS1 transgenic mice given high-altitude hypoxia (HAH) in a hypobaric chamber on days 7–20 of gestation

showed that prenatal hypoxic mice exhibit a remarkable deficit in spatial learning and memory and a significant reduction in synapses. In the same work, a considerably elevated level of APP, a lower level of the Aβ-degrading enzyme neprilysin and an increased Aβ accumulation in the brain of prenatal hypoxic mice were also noted (Zhang et al., 2013a). In conclusion, robust experimental evidence shows that obesity and other metabolic stress stimuli during very early prenatal stages can induce metabolic disorder and irreversible neuro-pathologic conditions in children (Muhlhausler et al., 2008).

3. Blood lipid disorders and AD

MS is characterized by high triglycerides and a low concentration of HDL cholesterol. Other lipoprotein abnormalities have been found in more detailed analyses of lipoprotein profiles, including increased lipoproteins and elevated apo-lipoprotein B, small LDL particles and small HDL particles (Grundy et al., 2005, 2006). MS-associated mixed hyperlipidemia is a classic risk factor for atherosclerotic cardiovascular disease (ASCVD). However, some clinical studies have reported that low HDL levels could be a risk factor for the development of some types of dementias, including AD (Bonarek et al., 2000; Di Paolo and Kim, 2011; Panza et al., 2006; Vijayaraghavan, 2010). Furthermore, clinical studies in AD patients have reported a decrease in HDL in both serum and cerebrospinal fluid (CSF), which was associated with the severity of AD (Merched et al., 2000; Mulder et al., 1998; Roher et al., 2002). Conversely, high HDL cholesterol levels in elderly individuals have been associated with a decreased risk of AD (Reitz et al., 2010). These data support a relationship between lipid disorders and AD.

The molecular mechanisms by which dyslipidemias are associated with an increased risk of some neurodegenerative diseases remain unclear (Vance, 2012). However, a critical role for factors including membrane cholesterol has been proposed. Genetic studies indicated that the expression of allele 4 of ApoE, the key protein in lipid metabolism, is a risk factor for AD, which led to the suggestion that cholesterol is a risk factor for AD (Liu et al., 2013; Roses, 2006; Zlokovic, 2013). Cholesterol is an important component of cellular membranes and is critical for maintaining membrane structure and function (Goedeke and Fernandez-Hernando, 2012). Increased cholesterol can stimulate the processing of APP and increase the production and aggregation of Aβ *in vivo* and *in vitro* (Rushworth and Hooper, 2010). In addition, cholesterol-lowering drugs (statins) concurrently reduce Aβ production (Fassbender et al., 2001). Moreover, increases in Aβ modulate the neuronal metabolism of cholesterol and stimulate the hyper-phosphorylation and accumulation of *tau* protein, which triggers the neuropathology of AD (Sparks et al., 2011).

Intense research is focused on the protection against AD conferred by statins and other lipid-lowering drugs (Shepardson et al., 2011a,b; Zhang et al., 2013b). Several studies indicate that the intake of statins is associated with a reduced risk of developing AD (Barone et al., 2013). One possible mechanism by which statins may exert a beneficial effect is an increase in the expression of the insulin-degrading enzyme (IDE), a protein that could increase the degradation of extracellular Aβ (Haag et al., 2009; Tamboli et al., 2010). In addition, recent studies on the effects of statin treatment on oxidative stress levels found a modulation of the heme oxygenase/biliverdin reductase (HO/BVR) system in the CNS, which is neuro-protective and has potential therapeutic benefit in AD (Barone et al., 2013, 2014). However, further studies are needed to address the risks and benefits of cholesterol-lowering drug therapy in AD.

Different genes that confer susceptibility for developing AD have been identified (Bertram et al., 2010; Bettens et al., 2013), among which we can mention ApoE4, apolipoprotein J (ApoJ), ATP-binding cassette subfamily A member 7 (ABCA7) and the sortilin-receptor (SORL1); all of these genes are related to the metabolism and biology of cholesterol (Ikonen, 2008).

The ApoE4 allele is globally associated with a set of factors such as hyperlipidemia, atherosclerosis, coronary heart disease, stroke and T2DM (Lahoz et al., 2001; Mahley and Rall, 2000; Malek-Ahmadi et al., 2013). There are three common alleles of ApoE: ApoE3 is the most common allele with a 78% prevalence in the general population; ApoE 4 is at 15%; and ApoE 2 is at 7% (Mayeux et al., 1993; Ward et al., 2012). The proportion of different ApoE alleles varies between racial and ethnic groups. In 1993, Roses and colleagues reported the association of ApoE4 with late-onset familial AD (Roses, 2006; Strittmatter et al., 1993b). The ApoE genotype affects the rate of disease expression, clinical dementia, and neuro-pathological markers. Aggregate data compiled in many laboratories demonstrate that ApoE4 is correlated with an earlier presence and greater density of amyloid plaques in patients meeting the criteria for AD (Strittmatter et al., 1993a,b). The ApoE4 allele frequency increases in lower categories of dementia, where the plaque counts are insufficient for the diagnosis of definitive AD. ApoE exhibits variable binding to the Aβ peptide (Barger et al., 2008; Poirier, 2000; Thal et al., 1997) and associates with neuritic plaques in AD (Morgan et al., 2004). Moreover, ApoE may perform multiple metabolic functions in the brain and is present in the extracellular space as a free and bound protein. It is also found in some neurons, both in the cytoplasm and in the intra-vesicular space of endosomes, lysosomes and peroxisomes (Han et al., 1994a,b; Sanan et al., 1994; Zlokovic, 2013). This latter localization in several intracellular sites suggests multiple metabolic functions for ApoE.

4. Hypertension and AD

Hypertension is defined as persistent systolic blood pressure (BP) $\geq$140 mm Hg and diastolic BP $\leq$90 mm Hg. Overall, approximately 20% of the population worldwide has hypertension, and its incidence is increasing. In a classical view, hypertension is considered a risk factor for several diseases, including hemorrhagic and ischemic stroke. Several studies have reported that BP is increased in AD patients, even decades before the onset of the disease (Kalaria et al., 2012; Nickey et al., 2003; Skoog and Gustafson, 2006).

Epidemiological studies suggest that hypertension during midlife leads to dementia and cognitive decline and might increase the risk of AD. However, the possible mechanism of this interaction is unclear (Duron and Hanon, 2008a,b; Kivipelto et al., 2002; Watts et al., 2013). One possibility is that chronic high BP leads to several pathological alterations, including hypertrophy of smooth muscle cells, changes in arterial resistance and modulation of the hemodynamic equilibrium in brain tissue. Together, these processes increase the risk of cerebrovascular disease and may increase the risk of AD (Caselli et al., 2011; Wiesmann et al., 2013), possibly through a mechanism involving small vessel disease, ischemia, oxidative stress and inflammation (Kalaria et al., 2012; Prins et al., 2005; Skoog and Gustafson, 2006). Alternatively, in people with high BP, increased numbers of NFTs and amyloid plaques in post-mortem brains have also been observed, suggesting a direct link between high BP and AD (Papassotiropoulos et al., 2003). In addition, hypertension in aging rats induced changes in the hippocampal expression of genes including APBA3, APBB1 and APLP1 by altering APP amyloidogenic processing (Csiszar et al., 2013).

Another possible mechanism to explain the association between hypertension and AD is the effect of the renin–angiotensin system (RAS), which is a hormonal system that regulates BP and water level balance (Min et al., 2009). The key

effector precursor molecule of RAS is angiotensinogen, a protein produced mainly in the liver. Angiotensinogen is cleaved to a 10 amino-acid peptide, angiotensin (Ang I), by a unique aspartyl protease called renin, which is produced by the juxtaglomerular apparatus (JGA) in the kidney. The angiotensin-converting enzyme (ACE) then cleaves Ang I into a smaller, highly active 8 amino-acid peptide, angiotensin II (Ang II). Ang I is inert, while Ang II signals through two receptors: the AT1 and AT2 receptors, which have different functions. In general, salt reabsorption and vasoconstriction mechanisms are stimulated by Ang II and are mediated by the AT1 receptor. In addition, the local tissue production of Ang II is linked to a variety of diseases, including hypertension, atherosclerosis and kidney disease (Fig. 3B) (Atlas, 2007; Fyhrquist and Saijonmaa, 2008; Ribeiro-Oliveira et al., 2008).

The brains of patients with AD exhibit elevated levels of ACE, Ang-II and angiotensin II receptors (AR-II) (Arregui et al., 1982; Savaskan et al., 2001). ACE decreases the aggregation of Aβ and the formation of Aβ fibrils and activates the proteolytic cleavage of Aβ (Hu et al., 2001). Ang-II also inhibits apoptosis in hippocampal neurons (Kakinuma et al., 1997), most likely *via* the AT2 receptor, which is also expressed in the brain (Ohshima et al., 2013; Rosenstiel et al., 2002). α/β adrenergic agonists (catecholamines) are a second class of BP hormone regulators. Recent studies have demonstrated that $A\beta_{(25-35)}$ and $A\beta_{(10-35)}$ induced a positive chronotropic effect in the cardiac contraction assay *via* the α1-adrenergic receptor (Haase et al., 2013), which suggests a possible bidirectional mechanism: from AD to hypertension and from hypertension to AD (Csiszar et al., 2013).

Interestingly, AD-like neuropathology has been found in an experimental model of hypertension called "transverse aortic coarctation" (TAC). Mouse models of hypertension (TAC and Ang-II infusion) show an increased permeability of the blood–brain barrier (BBB) in the cortex and hippocampus. More interestingly, in the same area, hypertensive mice showed positive staining for anti-Aβ antibodies and the presence of Aβ-like fragments. Finally, when mice were analyzed after passive immunotherapy with anti-Aβ IgG, a marked reduction in Aβ immunoreactivity in both the cortex and hippocampus was observed (Carnevale and Lembo, 2011; Gentile et al., 2009). This murine model of hypertension that develops a type of AD provides an excellent opportunity to study the molecular mechanisms that mediate the cross-talk between both diseases.

5. Insulin resistance, type 2 diabetes and AD

T2DM is one of the most prevalent chronic diseases related to MS, affecting over 200 million people worldwide (Ginter and Simko, 2012a,b). T2DM is characterized by chronic high glucose in the blood (hyperglycemia) caused by the inability of the body either to produce insulin or to produce enough insulin and/or by the inability of cells to respond to the insulin produced by the pancreas. Chronic hyperglycemia eventually leads to the failure of several tissues, including the kidney, heart, eye and brain (Ginter and Simko, 2012b). In the brain, chronic hyperglycemia leads to failures in the micro- and macro-vasculature, which has been associated with cognitive dysfunction. Thus, T2DM is a risk factor for the onset of AD (Adeghate et al., 2013; Ahtiluoto et al., 2010; Sanz et al., 2009; Tennant and Brown, 2013). However, the cellular mechanisms that associate T2DM and AD are unknown.

Some reports support the idea that the deleterious effects of hyperglycemia on the endothelium are critical in the relationship between T2DM and AD, and both vascular dependent and vascular independent factors have been described in this context (Akinyemi et al., 2013; Sato and Morishita, 2013; Takeda et al., 2011). Abnormal glucose metabolism and oxidative stress contribute to the formation of advanced glycation end products (AGE), which are chemically modified products of a sugar reduction reaction. Abnormal glucose metabolism and oxidative stress also contribute to the generation of *Amadori-modified* proteins, which are intermediate products of non-enzymatic glycation that increase in the serum as a result of chronic hyperglycemia (Baumann, 2012; Song and Schmidt, 2012). Some AGEs, including pyrraline and Nε-(carboxymethyl) lysine (CML), lysine-residue modified products and argpyrimidine, have been characterized in diabetes; some of these products also commonly occur in AD (Rabbani and Thornalley, 2008). AGE immunoreactivity is present in both Aβ plaques and NFTs in hippocampal neurons from patients with AD (Franke et al., 2013). Several reports have demonstrated that AGE are able to induce the glycation of Aβ and *tau*, stimulating the aggregation of these proteins and leading to the neuropathology of AD (Currais et al., 2012; Miranda et al., 2000; Yan et al., 1994). Conversely, *Amadori* products can activate several signaling pathways that are associated with inflammation, apoptosis and oxidative stress and cause vascular damage (Murray et al., 2011; Sato et al., 2006a,b). *Amadori* products have been found to be increased in the CSF of AD patients; one study reported that the levels of CSF Amadori product were 1.7-fold higher in AD patients than they were in controls (Shuvaev et al., 2001).

Another important factor that may be associated with T2DM and AD is the change in brain insulin levels. The multiple functions that insulin performs in the brain have been known for some time and include the regulation of memory processes, survival, neuronal plasticity and activation of NMDA receptors in synaptic regions (Fig. 3C) (Dou et al., 2005; Porte et al., 2002, 2005; Wozniak et al., 1993). The insulin pathway is initiated by the interaction of insulin with the insulin receptor (IRs). These receptors have been described in several tissues including adipose tissue, muscle and brain. Moreover, in some clinical Alzheimer studies, a decrease in insulin-pathway components has been described, suggesting a role for insulin signaling in the development of AD (Craft et al., 2013; Havrankova et al., 1978; Medhi and Chakrabarty, 2013; Messier and Teutenberg, 2005).

The decrease in cognitive functions in AD is associated with a loss of synaptic function, mainly in the hippocampus (Selkoe et al., 2012). Interestingly, this structure is one of the brain regions with higher IR expression. Some studies have shown that the administration of insulin by intranasal and intra-cerebroventricular routes leads to an improved formation of spatial memory, modulating hippocampal activity and inducing the recovery of cognitive function in patients with AD (Freiherr et al., 2013; Haj-ali et al., 2009; Holscher, 2014; Park et al., 2000). Insulin is associated with glucose metabolism, which is critical for brain function because neurons are dependent on glucose as their energy source. Therefore, the deregulation of insulin signaling leads to neuronal energy deficiency, which increases the vulnerability of neurons to oxidative stress or other injuries. In fact, AD patients have cerebral glucose hypometabolism, most likely due to impairments of insulin signaling and distorted thiamine metabolism (Chen and Zhong, 2013; Messier and Teutenberg, 2005; Wu et al., 2008). In this respect, it is important to note that insulin signaling through IR leads to the activation of PI3K and later Akt, a pathway that inhibits glycogen synthase kinase-3β (GSK-3β) activity (Cohen and Frame, 2001). GSK-3β is an enzyme whose activity is increased in AD (Hooper et al., 2008; Leroy et al., 2007). Moreover, GSK-3β is known to contribute to the formation of NFTs and the production of Aβ (Asuni et al., 2006; Lovestone et al., 1994; Pei et al., 1997). Various authors have suggested that GSK-3β may be a critical interaction point between both neuropathological processes (Caricasole et al., 2004; De Ferrari and Inestrosa, 2000; Inestrosa and Arenas, 2010; Lovestone, 2001). Various recent studies have shown that the inhibition of GSK-3β is a logical anti-AD strategy (Ly et al., 2013; Parr et al., 2012) and, recently, an anti-T2DM

strategy (Seto et al., 2012). Regarding the latter point and considering how common cross-talk between signaling pathways is, it is clear that GSK-3β deserves a key position in the progression of both AD and T2DM (Gao et al., 2012). In patients with AD, fasting leads to larger decreases in insulin levels in plasma and CSF. If insulin levels are increased, enhanced cognitive behavior is observed in these patients. However, if hyperglycemia does not increase the levels of insulin, no enhancement of cognitive function in patients with severe AD is observed (Baker et al., 2011; Craft et al., 1993, 1998, 2013; De Felice, 2013; Schioth et al., 2013).

Some reports have proposed that insulin could regulate the metabolism of proteins related to AD, including APP and *tau* (Bitel et al., 2012; De Felice, 2013; Tokutake et al., 2012; Umegaki, 2012). Insulin can potentially modulate the balance between Aβ production and degradation in the brain through the activation of the IDE, a metalloprotease involved in the degradation of extracellular Aβ. However, IDE degrades insulin and decreases insulin levels, which could reduce the degradation of Aβ, thereby reducing its accumulation (Qiu et al., 1998; Vekrellis et al., 2000). Furthermore, insulin was shown to increase the extracellular levels of the Aβ fragments $A\beta_{1-40}$ and $A\beta_{1-42}$ in mouse neuroblastoma (Gasparini et al., 2002). Insulin alters the extracellular concentration of Aβ by two independent mechanisms: inhibiting the extracellular degradation of Aβ by IDE and stimulating Aβ secretion (Gasparini et al., 2001; Vignini et al., 2013). Overall, these results indicate that insulin could play an important role in regulating *tau* protein, Aβ and APP metabolism in neurons (Townsend et al., 2007). Thus, dysfunction of insulin signaling might be involved in the pathological events that lead to the development of the neurofibrillary lesions and amyloid plaques that are characteristic of AD brains (De Felice, 2013; De Felice and Ferreira, 2014; de la Monte, 2012a,b; Steculorum et al., 2014). Thus, it has been demonstrated a direct relationship between AD and the dysregulation of glucose metabolism through an insulin resistance mechanism (De Felice et al., 2014; Ferreira et al., 2014; Stranahan et al., 2008b). The possible protective role of brain insulin in the onset of AD (De Felice et al., 2009) has led to the suggestion that AD could represent a "type 3 diabetes". This idea supports the use of drugs to control glucose utilization in AD patients, for example exenatide (Accardi et al., 2012; Akter et al., 2010; Bomfim et al., 2012; de la Monte and Wands, 2008; Hoyer, 2004; Li et al., 2012). Of note, a recent report by Yang (et al.), shows that the subcutaneous administration of liraglutide, a GLP-1 receptor agonist that improves glucose homeostasis, ameliorates AD-associated tau hyperphosphorylation in rats with T2DM (Mehla et al., 2014; Yang et al., 2013). Liraglutide also induces a highly significant decline in astrocytosis and microglial numbers associated with both plaques and IR pathology (aberrant phosphorylation of IRS-1 and pS616) in a mouse model of AD (Long-Smith et al., 2013).

Peroxisome proliferator-activated receptors (PPAR) are a key family of nuclear receptors involved in metabolic homeostasis. There are three known PPAR isoforms: α, β and γ (Zolezzi and Inestrosa, 2013). The pleiotropic function of these receptors includes the promotion of glucose uptake, the increase of fatty acid oxidation and the enhancement of insulin action (Gelman et al., 2007). Thiazolidinediones (TZDs) are PPAR-γ agonists used as anti-diabetic drugs (Cariou et al., 2012). We previously demonstrated that the activation of PPAR-γ by TZDs protects rat hippocampal neurons against oxidative stress and Aβ insults by various mechanisms, which include GSK-3β inhibition, increased expression of the Wnt signaling gene Bcl-2 (an anti-apoptotic protein) and prevention of mitochondrial dynamic deregulation (Fuenzalida et al., 2007; Inestrosa et al., 2005a; Zolezzi et al., 2013). In an AD transgenic mouse model (APPswe/PS-1), we also demonstrated that both PPARγ and α agonist administration reduced spatial memory impairments, synaptic failure and neurodegeneration in the cortex and hippocampus (Inestrosa et al., 2013). These studies support the idea that PPAR stimulation is a possible therapeutic anti-AD strategy (Cramer et al., 2012; Heneka et al., 2011; Zolezzi and Inestrosa, 2014). In summary, several studies have revealed that a number of oral antidiabetic drugs can improve cognition in patients with MCI; however, the data are not clear for AD (Alagiakrishnan et al., 2013; Huang et al., 2014).

Finally, another interesting set of data was recently obtained from the study of a natural animal model of AD, the South American rodent *Octodon degus* (*O. degus*). In this particular rodent, we found that age is associated with Aβ deposition, mimicking AD and related tauopathies. The *O. degus* Aβ peptide sequence has a high degree (97.5%) of homology with human Aβ (Fig. 4) (Inestrosa et al., 2005b). Interestingly, Aβ deposits in blood vessel walls precede the deposits of Aβ and *tau* in the hippocampus of 3-year-old animals (van Groen et al., 2011). Neural plasticity impairments are observed before the appearance of amyloid deposition (Ardiles et al., 2012). Coincidentally, the *O. degu* also develops insulin resistance (Opazo et al., 2004). Thus, this caviomorph rodent has a predisposition to T2DM as a result of impaired insulin action (Brown and Donnelly, 2001; Datiles and Fukui, 1989). In addition, amyloidosis in the Langerhans islet cells of this animal has been reported (Nishi and Steiner, 1990). This is the single most typical islet alteration in T2DM and is present in over 90% in of T2DM patients (Hoppener et al., 2000; Hoppener and Lips, 2006). These data show that the *O. degus* has great potential as a natural model for studying the connections among T2MD, insulin-resistance, AD and MS development (Braidy et al., 2012; Jackson et al., 2013; Tarragon et al., 2013).

6. Role of Wnt signaling in the relationship between MS and AD

Wnt is a conserved intracellular signaling pathway with important functions in almost all tissues, including the liver, muscle, kidney and brain. Some of these functions include cell proliferation, polarity, apoptosis, inflammation and differentiation (Nusse and Varmus, 2012). Wnt signaling has been related to several diseases including cancer, AD, autism, schizophrenia, Parkinson, fatty liver disease and fibrosis (Anastas and Moon, 2013; Cisternas et al., 2013; Clevers and Nusse, 2012; De Ferrari et al., 2013; Inestrosa et al., 2012; Inestrosa and Varela-Nallar, 2014; Oliva et al., 2013; Rosso and Inestrosa, 2013). The paramount importance of Wnt signaling is clearly exposed by genetic studies in which mouse mutations that led to the loss of function of Wnt components caused drastic changes in the phenotype or death in embryonic stages (Anastas and Moon, 2013; Cisternas et al., 2013; Inestrosa et al., 2012; Kim and Kang, 2012; Marchetti and Pluchino, 2013; Nusse, 2012; Oliva et al., 2013; Zimmerman et al., 2012).

Wnt signaling is initiated by the action of Wnt ligands, which belong to a conserved family of cysteine rich glycoprotein. In humans, 19 Wnt ligand genes have been described, each with a different expression pattern and function (Clevers and Nusse, 2012; Nusse and Varmus, 2012). The signaling activated by each Wnt ligand can be divided into two types: canonical or Wnt/β-catenin and non-canonical or β-catenin-independent pathways. However, is necessary to keep in mind that one Wnt ligand can activate more than one pathway, depending of the expression of downstream components and other unknown factors (Niehrs, 2012).

6.1. The Wnt/β-catenin pathway

Activation of the Wnt/β-catenin pathway occurs during embryogenesis in several tissue types, including muscle, brain

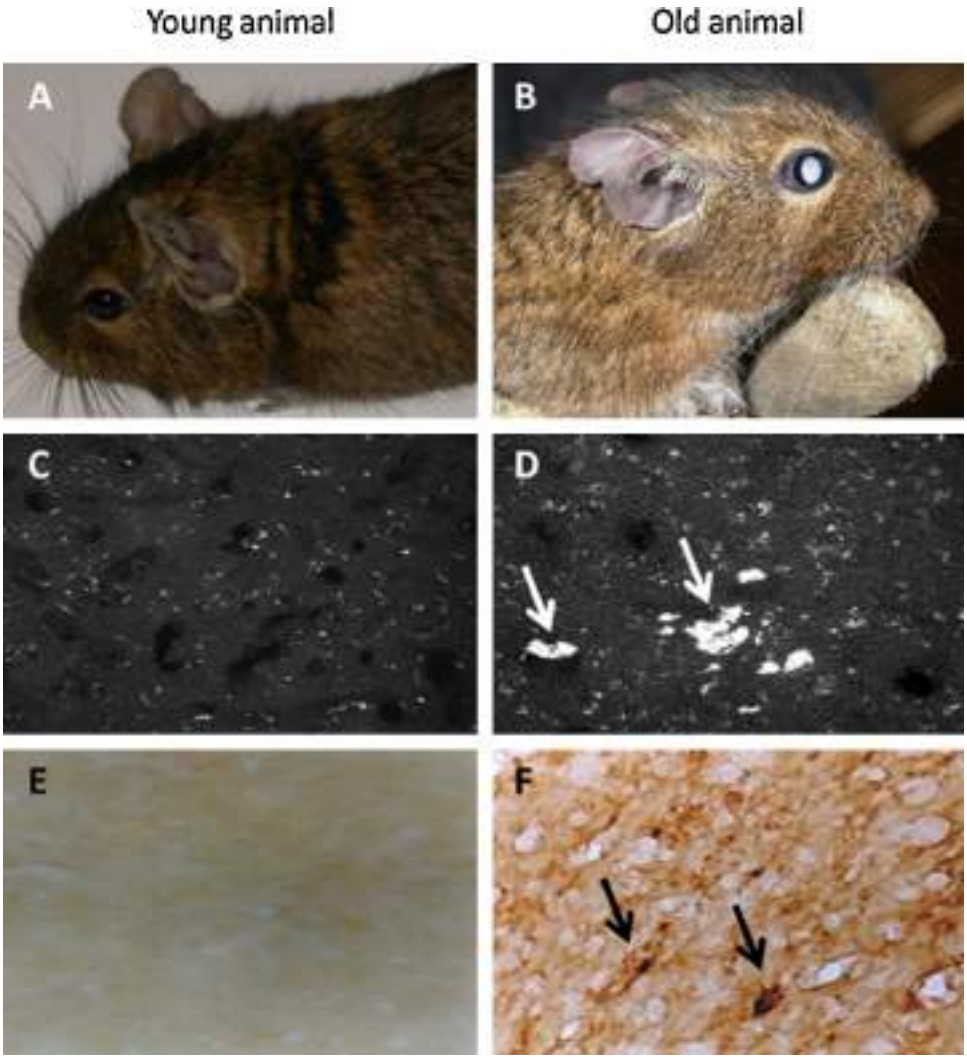

Fig. 4. *Octodon degus*, a natural model of AD and T2D. These pictures show two different ages of *Octodon degus*. (A) Young animal (≤24 months) without cataract formation. (B) Old animal (≥24 months) that develops cataracts, probably because of the advanced glycation of crystalline lens proteins. (C, D) Coronal section of the cortex of the *O. degus* brain with thioflavin-S staining, young animal (left) did not show plaque formation and old animal (right) forms senile plaques (white arrow). (E, F) Immunohistochemistry coronal section of the cortex of *O. degus* with Aβ antibody, young animal (left) without plaque formation and old animal (right) with senile plaques (black arrow).

and kidney. In adult stages, the activation of Wnt signaling is related to proliferation and differentiation. The failure of these functions is directly related to cancer progression (Anastas and Moon, 2013; Behari, 2010; Brack et al., 2008; Budnik and Salinas, 2011; Colombres et al., 2008; Pulkkinen et al., 2008). The canonical Wnt pathway begins with the binding of the Wnt ligand to a member of the Frizzled (Fzd) receptor family, of which 10 members have been described in vertebrates (Wang et al., 2006). The Wnt–Fzd interaction requires the LDL-receptor-related proteins 5/6 (LRP5/6), which act as co-receptors for the Wnt ligand. This complex then recruits the scaffold protein disheveled (Dvl). Intracellularly, the canonical Wnt pathway requires the intracellular accumulation of β-catenin, whose levels are normally kept low by the action of a so-called "destruction complex" formed by several proteins, including the scaffold protein Axin, Adenomatous polyposis coli (APC), casein kinase I and the enzyme glycogen synthase kinase-3β (GSK-3β). This destruction complex leads to the hyper-phosphorylation of β-catenin, stimulating its destruction by the proteosomal pathway (Niehrs, 2012). Activation of the canonical Wnt pathway leads to the dissociation of the β-catenin destruction complex by a series of phosphorylations that together lead to the inactivation of GSK-3β. β-Catenin then accumulates and translocates to the nucleus, where it interacts with the T-cell specific transcription factor (TCF) and the lymphoid enhancer-binding factor (LEF), thus inducing the expression of Wnt target genes including Cyclin D, c-jun, Ca^{2+}–calmodulin-dependent protein kinase type IV, endothelin-1, BMP4 and interleukin-8, to name just a few (Fig. 5) (Arrazola et al., 2009; Clevers and Nusse, 2012; Hodar et al., 2010). Wnt signaling is modulated not only by the presence or absence of Wnt ligands but also by secreted antagonists that directly interact with ligands. These inhibitors of Wnt signaling include the secreted Frizzled-related proteins (sFRPs) (Bovolenta et al., 2008). In mammals, the sFRP family consists of 5 members, termed sFRP1–5 (91–98% amino acid identity between human and murine sequences). Other antagonists engage directly with receptors, such as the Dickkopf (Dkk) family of secreted glycoproteins. Dkk1, Dkk2 and Dkk4 bind to LRP5/6, thereby preventing its interaction with Wnt ligands (Niehrs, 2012). The tight regulation of the spatiotemporal expression of Wnt ligands by Wnt modulators, such as sFRPs and Dkks, is also likely to be involved in the regulation of a variety of cellular functions and critical processes mediated by canonical Wnt signaling.

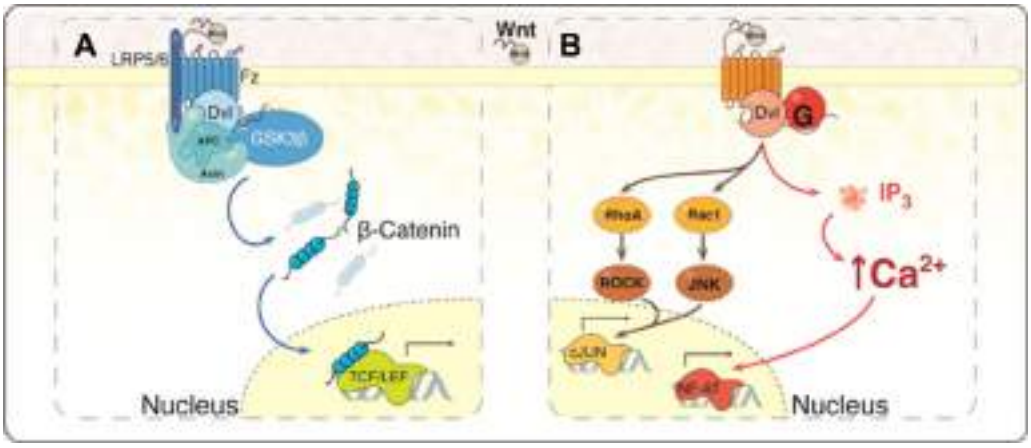

Fig. 5. The main signaling pathways of Wnt signaling. (A) Activation of the canonical Wnt signaling pathway leads to inhibition of GSK-3β by dissociating the enzyme from a multiprotein complex. This results in the stabilization of β-catenin and subsenquently its traslocation into the nucleus where it binds to the TCF/LEF transcription factors that initiate Wnt target gene transcription. (B) The non-canonical Wnt signaling pathways known as Wnt/PCP and the Wnt/Ca^{2+} pathways. In the latter, Wnt ligands increase Ca^{2+} and activate CaMKII and PKC, on the other hand, in the Wnt/PCP pathway, monomeric GTPases activate (JNK and ROCK) and they subsequently modify the cytoskeleton.

6.2. The non-canonical Wnt signaling

There are at least two other pathways activated by Wnt ligands in a β-catenin independent manner, the planar cell polarity pathway (Wnt/PCP) and the Wnt–calcium signaling pathway (Wnt/Ca^{2+}). In the Wnt/PCP pathway, the Wnt–Fz dependent recruitment of Dvl leads to the activation of small GTPase proteins, such as Rho and Rac, which subsequently activate the c-Jun N-terminal kinase (JNK) pathway. These proteins can either signal the nucleus or modify cytoskeletal stability by affecting the phosphorylation of microtubule associated proteins (MAPs). These proteins are also able to interact with actin-regulator proteins. The activation of JNK activates transcriptions factors, leading to the expression of target genes (Barrow, 2006; Descamps et al., 2012; Simons and Mlodzik, 2008). Finally, in the Wnt/Ca^{2+} pathway, signaling downstream of Dvl stimulates trimeric G proteins and the enzyme phospholipase C (PLC), which increase the production of inositol triphosphate (IP3), thus triggering an increase in intracellular Ca^{2+}. As a consequence, Ca^{2+}-dependent proteins such as protein kinase C (PKC), calcium–calmodulin dependent protein kinase II (CaMKII) and the phosphatase calcineurin are activated. Some of these enzymes regulate the transcription factor NF-AT, thus promoting the expression of specific target genes (Fig. 5) (Inestrosa et al., 2012; Nusse and Varmus, 2012; Toledo and Inestrosa, 2010; Varela-Nallar et al., 2010). Non-canonical Wnt signaling also affects mitochondrial physiology, thereby modulating mitochondrial dynamics (fusion-fission) (Silva-Alvarez et al., 2013).

6.3. Wnt signaling and AD

Over a decade ago, we and other groups established a strong relationship between a loss of function of Wnt signaling and neuronal damage in AD (De Ferrari et al., 2003; De Ferrari and Inestrosa, 2000; Inestrosa and Toledo, 2008; Purro et al., 2012; Vargas et al., 2014). Different reports have shown that Wnt signaling components are affected in AD: (1) β-catenin levels are reduced in patients carrying presenilin-1-inherited mutations (Zhang et al., 1998); (2) the exposure of cultured hippocampal neurons to Aβ results in inhibition of canonical Wnt signaling (Alvarez et al., 2004); (3) Dkk,1 a Wnt antagonist induced by Aβ, aggregates in hippocampal neurons (Caricasole et al., 2003, 2004); (4) apo-lipoprotein E (apoEe4), an AD risk factor, inhibits canonical Wnt signaling (Caruso et al., 2006); (5) a common genetic variation within LRP6 leads to disease progression (Alarcon et al., 2013; De Ferrari et al., 2007); (6) Dkk1 reversibly reduces the amount of synaptic proteins and the number of active pre-synaptic sites, inducing synaptic disassembly at pre- and postsynaptic sites (Purro et al., 2012); (7) clusterin, a susceptibility factor for late-onset AD (Harold et al., 2009), induces Dkk-1 expression (Killick et al., 2014); and (8) Dkk1 not only antagonizes Wnt/β-catenin canonical signaling but also permits Wnt ligands, in the absence of LRP5/6, to bind Fz and activate non-canonical pathways, in particular, the Wnt/Planar Cell Polarity (Wnt/PCP) pathway, which acts *via* JNK to regulate the expression of Aβ target genes involved in *tau* phosphorylation and neuronal death (Killick et al., 2014). Taken together, these findings suggest that Wnt signaling is important in AD pathogenesis. Considering Wnt's role in synaptic function, a reduction in or deregulation of its components may contribute to the synaptic dysfunction characteristic of the early stages of AD (Inestrosa and Varela-Nallar, 2014; Oliva et al., 2013; Rosso and Inestrosa, 2013; Varela-Nallar et al., 2010). Within the same context, cardiometabolic risk factors has been associated with Parkinson's disease (PD), including hypertension and obesity (Cassani et al., 2013; Cereda et al., 2013; Chen et al., 2014; Schelp et al., 2012). In a Wnt context, accumulating data show that a dysregulation of Wnt signaling also occurs in PD, a disorder characterized by the progressive loss of dopaminergic (DA) neurons in *substantia nigra* of the midbrain (Arenas, 2014; L'Episcopo et al., 2014; Parish and Thompson, 2014). Typical *tau* pathology has been observed in post-mortem brains of PD patients with *PARK8* mutations, this suggest a connection with GSK-3β polymorphisms previously discovered in PD (Berwick and Harvey, 2012). Finally, early studies show that Wnt5a-treated neural stem cells lead to efficient source of DA neurons for possible therapy in PD (Parish et al., 2008). Therefore the association between Wnt signaling and neurodegenerative diseases extend not only to AD, but also included Parkinson's disease.

6.4. Wnt signaling and adipogenesis

Some evidence suggests a role for Wnt signaling in various mechanisms associated with MS. For example, adipogenesis can be reversed by the activation of the canonical Wnt signaling pathway. The suggested mechanism posits that Wnt signaling inhibits the transcription factor CCAAT/enhancer binding protein α (C/EBPα) and PPAR-γ signaling (Isakson et al., 2009; Ross et al., 2000). In this context, a series of studies showed that the ligand Wnt10b

primarily inhibits the development of white and brown fat by both β-catenin dependent and β-catenin independent mechanisms. The overexpression of Wnt10b in *ob*/*ob* mice prevented the development of the obese phenotype, indicating that the permanent activation of the Wnt pathway prevents obesity in this model (Kennell and MacDougald, 2005; Longo et al., 2004; Wright et al., 2007). Recent studies by a different group have fully confirmed these findings from an opposite perspective, using endogenous inhibitors of the Wnt pathway such as Dkk1 or antagonists such as bone morphogenetic protein 4 (BMP-4), which promote adipogenesis (Gustafson and Smith, 2012). Studies using preadipocytes with or without knockdown of the Wnt co-receptors LRP5/6 demonstrate a cross-talk between insulin and Wnt signaling (Palsgaard et al., 2012). Similarly, another study demonstrated that LRP6 (+/−) animals on a HFD are protected from diet-induced obesity and hepatic and adipose insulin resistance compared with their wild-type littermates (Liu et al., 2012). In addition to these data, evidence in human tissue demonstrates that the levels of endogenous inhibitors of the Wnt pathway such as sFRP1, sFRP4 and sFRP5 are elevated in obese and insulin-resistant patients and deregulated in adipose tissue (Carstensen et al., 2013; Ehrlund et al., 2013; Lagathu et al., 2010). Recent reports show that sFRP is increased in response to an initial weight gain. Sfrp1 deficient (sfrp1−/−) mice fed an HFD exhibited an increase in body mass accompanied by an increase in body fat percentage, visceral white adipose tissue mass and adipocyte size. The study authors postulated an underling mechanism involving increased macrophage infiltration and expression of pro-inflammatory markers including IL-6, Nmnat and Tgf-β2 (Ehrlund et al., 2013; Gauger et al., 2013). Finally, it is interesting to note that the activation of the Wnt pathway, particularly for obesity and the accumulation of visceral fat, could be very beneficial in the context of AD (De Ferrari and Inestrosa, 2000; Inestrosa and Arenas, 2010). Common therapeutic approaches could possibly be developed, aiming for the same pharmacological target. In leptin-deficient mice, Wnt-LRP6 signaling is impaired in the hypothalamus, a region that controls food intake, suggesting that the Wnt pathway regulates obesity by controlling excessive food intake behavior (Benzler et al., 2013).

6.5. Wnt signaling and lipoprotein metabolism

Wnt signaling is associated with high levels of lipids in the blood and with ApoE. In AD, ApoE4 is a natural ligand of the LRP receptor family, and LRP 5 and 6 are co-receptors of the Wnt pathway (De Ferrari et al., 2007). In AD, the reduction in Aβ clearance is due to the failure of the interaction of ApoE4 with its receptor, LRP1 (Holtzman et al., 2012), because the levels of this receptor are reduced in AD brains (Kang et al., 2000). LRP1 has a high homology with the co-receptors of the Wnt (LRP5/6) pathway, one of which (LRP6) has been associated with the risk of AD. Recently, LRP6 has also been associated with MS risk and particularly with coronary disease (Singh et al., 2013; Xu et al., 2014). Other studies show that people with LRP6 (R611C) point mutations develop high plasma LDL, TG levels and NASH, which is the opposite of what happens when Wnt signaling is activated by Wnt-3a (Godoy et al., 2014b). It has also been proposed that ApoE and other lipoproteins may modulate the activity of the Wnt pathway (De Ferrari et al., 2007; Zilberberg et al., 2004). The β-catenin knockout mouse model with diet-induced non-alcoholic steatohepatitis shows higher levels of cholesterol and triglycerides in the liver compared with control animals (Behari et al., 2010). Wnt/β-catenin signaling is required for hepatocyte protection against oxidative stress-induced apoptosis in the chronic oxidative liver injury model triggered by 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) (Tao et al., 2013). Other authors have shown that β-catenin regulates many key players that are canonically associated with the regulation of oxidative stress in the liver, including cytochrome P450s and Glutathione S-transferases (Thompson and Monga, 2007). Therefore, the potential role of Wnt/β-catenin in the liver seems very interesting, and further studies are required to clarify the role of Wnt/β-catenin in normal and pathological states. New cholesterol-lowering drugs (simvastatin) enhance Wnt signaling *in vivo* and promote neurogenesis in cultured adult neural progenitor cells and in the dentate gyrus of adult animals (Robin et al., 2014).

6.6. Wnt signaling and hypertension

In relation to the interaction between hypertension and AD, Ang-II increases the mRNA expression of the frizzled 2 receptor (Fz2) in smooth muscle cells from rat aorta (Castoldi et al., 2005). Furthermore, disruption of the Wnt signaling pathway in a Disheveled ($Dvl^{-/-}$) double knockout mouse decreases secondary cardiac hypertrophy to blood pressure overload (Blankesteijn et al., 2008; van de Schans et al., 2007). Additionally, the inhibition of Wnt signaling, its symptoms were diminished after myocardial infarction (Daskalopoulos et al., 2013). However, more studies are needed to establish the role of Wnt signaling in the control of hypertension and the effect of this possible interaction with the onset of AD.

Hypertension leads to kidney fibrosis, which leads to kidney function failure and increases blood pressure in a chronic manner. The formation of fibrotic lesions in the kidney involves several pathways including angiotensin II and Wnt (Gonzalez et al., 2013; Rooney et al., 2011; Wang et al., 2011; Wuebken and Schmidt-Ott, 2011). In the kidneys, there is evidence that the Wnt pathway is indeed related to renal fibrosis based on the finding that β-catenin accumulates in the nuclei during the induction of the epithelial–mesenchymal trans-differentiation (EMT) in fibrotic disease (Kim et al., 2002). Moreover, transgenic mice carrying an oncogenic form of β-catenin develop severe polycystic lesions in the glomeruli, proximal tubules, distal tubules and collecting ducts (Saadi-Kheddouci et al., 2001). The administration of recombinant sFRP4 protein, a scavenger of the Wnt ligand, caused a reduction in tubular epithelial β-catenin signaling and suppressed the progression of renal fibrosis, with a decrease in the amount of fibronectin and α-smooth muscle actin proteins (He et al., 2009). The inhibition of canonical Wnt signaling by the administration of sFRP4, DKK1 and pyrvinium pamoate caused a reduction in β-catenin levels and ECM components that suppressed the progress of renal fibrosis (He et al., 2011; Surendran et al., 2005).

6.7. Wnt signaling and insulin resistance/type 2 diabetes

Finally, MS is also characterized by a deregulation of insulin metabolism, affecting the energy balance in several tissues including the brain and leading to the onset of T2DM (Craft et al., 2013). Several reports suggest a key role of GSK-3β in the interaction among AD, insulin metabolism and Wnt signaling (Cohen and Goedert, 2004). In this context, the canonical Wnt-3a ligand has been shown to enhance insulin signaling *in vitro*, activating metabolic enzymes such as Akt and leading to insulin sensitivity through an increase of insulin receptor substrate-1 (IRS-1) expression. Wnt-3a ligand also stimulates an increase in mitochondrial biogenesis through the same factor, IRS-1 (Yoon et al., 2010). These results are consistent with data from our laboratory that show that the non-canonical Wnt-5a ligand is also capable of affecting mitochondrial physiology and modulating mitochondrial dynamics (fusion–fission). In this sense, Wnt-5a ligand could play a role in the regulation of energy balance in AD (Silva-Alvarez et al., 2013). Additionally, the gastrointestinal

hormones incretins (GLP-1 and GIP-1) that enhance insulin secretion and that coincidentally are known neuroprotectors exert their insulin-enhancing action through the Wnt pathway, activating β-catenin indirectly and most likely *via* protein kinase A (PKA) (Bassil et al., 2014; Chiang et al., 2012). We highlight that both AD and T2DM, from a Wnt signaling perspective, are two pathologies that could benefit from the pharmacological activation of this pathway. Recent studies reported cross-talk between the Wnt signaling an insulin pathways. For example, in IR-overexpressing β-cells, the enhancement of β-catenin nuclear translocation and Wnt responsive genes including glucokinase (GK) and cyclin D1 ameliorate hyperglycemia in diabetic rats and promote β-cells proliferation (Kim et al., 2013; Wilson, 2013). Conversely, studies in HFD-induced obese animals found a lower expression of multiple molecular markers of insulin resistance and a decrease in β-catenin expression levels (Zhou et al., 2012). This phenomenon is likely a physiological response to high dietary sugar, as recently demonstrated in studies in *Drosophila*, in which increased canonical Wnt pathway activity upregulates insulin receptor gene expression to promote insulin sensitivity, completing the molecular circuit between glucose and Wnt signaling (Hirabayashi et al., 2013).

Over the last decade, several studies have tried to relate various Wnt components to the onset of T2DM. In 2006, Grant and colleagues showed for the first time that the transcription factor 7-like 2 (TCF7L2), which is activated by β-catenin canonical Wnt signaling, is a risk factor for T2DM; an intron polymorphism of TCF7L2 correlates with the onset of T2DM (Grant et al., 2006; Zeggini and McCarthy, 2007). Other studies have supported this link in several ethnic groups including populations from India, U.K., Europe, Asia and America (Chandak et al., 2007; Cho et al., 2009; Groves et al., 2006; Humphries et al., 2006; Miyake et al., 2008). A positive gene dosage effect is generally accepted, *i.e.*, 10% of individuals with two copies of the susceptibility allele have almost twice the risk of developing diabetes than do those with none (Zeggini and McCarthy, 2007). The direct molecular mechanism of the effect of TCF7L2 on the onset of T2DM is not fully understood. However, recent studies have shown that TCF7L2 plays a critical role in hepatic glucose production and that the expression of this protein is decreased in models of insulin resistance. For example, strong relationships exist between malondialdehyde (MDA) levels and different pathological stages of diabetes. Interestingly, RNA interference of TCF7L2 blocked the MDA-induced GSIS elevation (Wang et al., 2014b). Moreover, overexpression of TCF7L2 induced an increase in the glucose levels in the blood and increased insulin resistance. This latter effect could lead to the onset of T2DM, and chronic T2DM could increase the risk of AD (Cadigan and Waterman, 2012; Grant et al., 2006; Ip et al., 2012; Oh et al., 2012; Yang et al., 2012). Metformin also increased GLP1 secretion in L-cells and *db*/*db* mice. Metformin stimulates the nuclear translocation of β-catenin and TOPflash reporter activity and enhances the mutation of the TCF7L2 binding site on GLP1 (Kim et al., 2014).

Finally, Mahdi et al. (2012) found that secreted frizzled-related protein 4 (sFRP4) reduces insulin secretion and is a potential biomarker for islet dysfunction in T2DM. The authors identified a group of co-expressed genes associated with T2DM, reduced insulin secretion and elevated HbA1c levels after analyzing global microarray expression data from human islets from 48 individuals, including 10 with T2DM. This gene module was enriched for interleukin-1 (IL-1)-related genes. Mahdi et al. (2012) identified sFRP4 as a gene that is highly expressed in islets from patients with T2DM. The protein encoded by sFRP4 is an extracellular regulator of the Wnt pathway and plays a role in tissue development, cancer and neurogenesis (Bovolenta et al., 2008). Further study revealed that the expression and release of sFRP4 from islets was stimulated by IL-1β. Furthermore, elevated systemic sFRP4 levels led to reduced glucose tolerance as a result of the decreased islet expression of voltage-gated Ca^{2+} channels and suppressed insulin exocytosis. Interestingly, the levels of sFRP4 were elevated in the serum of patients a few years before they developed T2DM, which indicates that this protein has the potential to be used as a biomarker for T2DM (Mahdi et al., 2012). In these studies, we observed that some Wnt inhibitors may be an effective treatment for T2DM. Along the same line, an interesting study showed that blockade of Dkk2 (a small molecule or knockout Dkk−/−) improved the metabolic parameters in *db*/*db* mice, including decreased glucose and insulin levels and reduced GLP1 production in the intestine (Bomfim et al., 2012).

7. General conclusions

AD represents a critical health problem worldwide because it affects over half of the population over 85 years of age and involves a great financial cost to governments. AD is characterized by the accumulation of extracellular aggregates of Aβ peptide and intracellular NFTs. These neuropathological markers lead to the progressive loss of neuronal activity and finally dementia. Several groups have described the cellular processes affected in AD and the mechanisms that lead to the loss of cognitive function. However, the mechanisms involved in the onset of AD are still unknown.

In recent years, several reports have suggested that nutritional behavior could be an important triggering element in the pre-symptomatic stages of AD, contributing to the onset of AD in a progressive manner. MS is characterized by several conditions that are also reported in patients with AD, including obesity, an increased level of lipids in the blood, high blood pressure and T2DM.

In this review, we discussed the major molecular links between AD and MS, recapitulated the epidemiological evidence and gathered the experimental data that have been obtained from research conducted in both cellular models and transgenic animal models that present characteristics of both diseases. The evidence described supports the idea that MS is a risk factor for AD; however, the molecular mechanisms that control this association remain unknown. Understanding these mechanisms could be critical for the development of new therapeutic strategies to fight AD. In this context, new models to simultaneously study AD and the different components of MS are critical and necessary to understand the relationship between these two diseases *in vivo* (Table 2).

Table 2
Animal models proposed for studies of the MS and AD relationship.

Murine model	Model generation	Phenotype	References
Ob/*ob* transgenic mouse	Leptin double knockout (*leptin*$^{-/-}$)	Obese, insulin resistance, hypertension and elevated cholesterol levels	Ingalls et al. (1950) and Garza et al. (2008)
Hypertension related "AD-like" pathology murine model	Tranverse aortic coarctation (TAC)	Hypertension, brain Aβ deposition and cerebrovascular damage	Carnevale and Lembo (2011) and Gentile et al. (2009)
Model of fructose overload diet	High diet with fructose	Insulin resistance and hypertension	Agrawal and Gomez-Pinilla (2012)
Octodon degus natural model AD and T2D	*Wild-type*	AD-like pathologies, insulin resistance and atherosclerosis	Inestrosa et al. (2005a,b), Ardiles et al. (2012) and Homan et al. (2010)

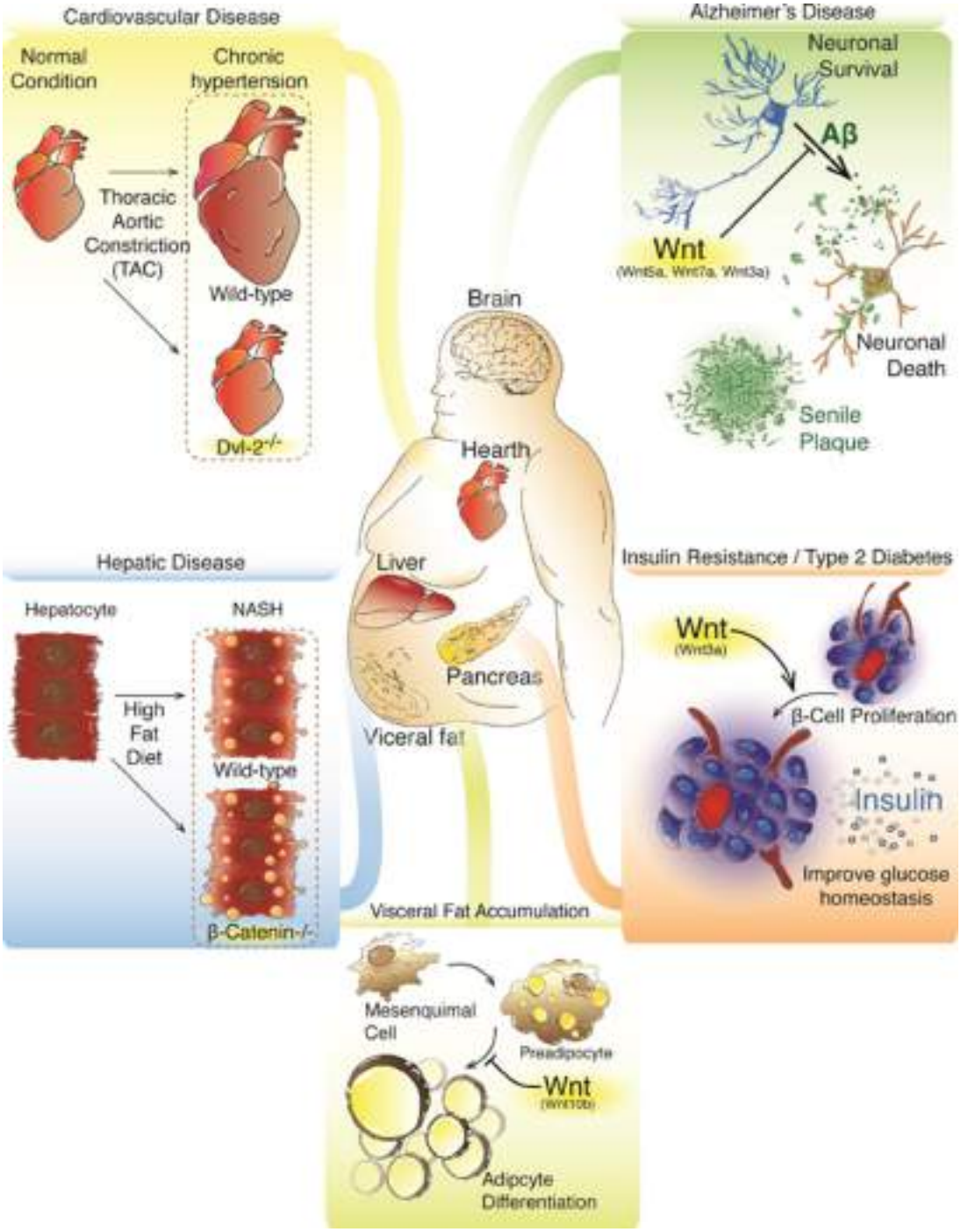

Fig. 6. Wnt signaling can modulate pathophysiological consequences of MS. In each case, specific changes in Wnt signaling modulate the course of the disease. *Cardiovascular disease*: the inhibition of Wnt signaling, mediated by Dvl-2 knock out ($Dvl^{-/-}$), attenuates the chronic effects of hypertension without the development of myocardial hypertrophy. *Hepatic disease*: the inhibition of Wnt signaling, mediated by β-catenin mutant knock out (β-$catenin^{-/-}$), leads to a more aggressive phenotype of non-alcoholic steatohepatitis (NAFLD). *Visceral fat accumulation*: canonical Wnt10b ligand, promotes the inhibition of preadipocyte differentiation with impairment of visceral fat expansion. *Type 2 diabetes mellitus (T2DM)*: activation of Wnt/β-catenin signaling with Wnt-3a increases pancreatic β-cell proliferation and enhances insulin secretion, resulting in an improvement of glucose homeostasis. *Alzheimer's disease*: canonical (Wnt-7a, Wnt-3a) and non-canonical (Wnt-5a) Wnt signaling activation enhances neuroprotection from neuronal damage triggered by Aβ fibers and oligomers.

Finally, we described the putative role of Wnt signaling in the relationship between AD and MS. Wnt signaling is critical for several cellular processes, and the deregulation of this pathway is associated with several diseases, including AD. Some evidence supports the participation of Wnt signaling in the modulation of several pathways in MS, including the regulation of adipogenesis, glucose metabolism, insulin production and the control of blood pressure. These multisystem effects of Wnt support the use of inhibitors or activators of this signaling pathway as potential therapeutic targets in both MS and AD (Fig. 6).

Conflicts of interest

The authors report no conflicts of interest.

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