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Review

Inflammatory risk factors and pathologies promoting Alzheimer's disease progression: is RAGE the key?

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Summary. Epidemiological studies reveal growing evidence that most cases of Alzheimer's Disease (AD) likely involve a combination of genetic and environmental risk factors. Identifying and validating these risk factors remains one of the most critical scientific challenges. Several diseases appear to have strong implications for neurodegeneration leading to dementia. This risk encompasses different forms of cardiovascular disease, carotid atherosclerosis, history of hypertension or high cholesterol, Type II diabetes, stroke or transient ischemic attack and brain trauma. However, the molecular pathways that are common and central in the progression of these diseases and AD are not yet elucidated. Unveiling these critical mechanisms at the molecular level is necessary for the development of therapeutic strategies aimed at preventing AD progression. The Receptor for Advanced Glycation Endproducts (RAGE) plays a key role in all the diseases that represent a risk for AD. RAGE-mediated signaling also contributes to neurodegeneration in AD, suggesting that it may mediate the effect of risk factors in promoting AD. We will summarize the current knowledge on the role of RAGE in pathologies promoting AD and in AD progression. We will also provide evidence showing the relevance of RAGE-induced inflammation as a risk pathway that is implicated in AD pathophysiology.

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Introduction

Alzheimer's Disease (AD) is the main cause of dementia among people age 65 and older, affecting more than 25 million people in the world currently. AD represents a major health problem and heavy economic burden in industrialized countries. AD is characterized by a progressive decline in cognitive function underlined by memory loss as well as personality changes. AD is a progressive neurodegenerative disorder associated with cognitive impairment and neuronal cell loss, and the pathology is characterized by the presence of several kinds of amyloid plaques and neurofibrillary tangles in the brain of AD patients, which are mainly composed by the beta amyloid (Aβ), derived from the proteolytic cleavage of the amyloid precursor protein (APP), and hyper-phosphorylated tau (Hardy and Selkoe, 2002). AD also shows a severe gliosis in the cerebral cortex and the hippocampus (Leclerc et al., 2010). Indeed, an increase in inflammatory responses such as an increase in production of proinflammatory mediators, microglial infiltration and activation, and levels of several SI00 calcium-binding proteins (S100B, S100A6, S100A9, and S100A12) in the AD brain has been recently reported.

Familiar AD is caused by mutations in APP and presenilins, which lead to Aβ overproduction (De Strooper et al., 2012; Haass et al., 2012). On the other hand, sporadic AD represents 95% of cases and its ultimate cause is still controversial (Kern and Behl,

2009). Although several reports, including our own, demonstrate the role of toxic Aβ oligomers in promoting AD neuropathology (Lesné et al., 2006, 2008; Selkoe, 2008; Mazarguil et al., 2012) , our results indicate that other co-factors are implicated in Aβ oligomers-mediated toxicity in sporadic AD (Bjorklund et al., 2012; Crawford et al., 2012). Recent studies reveal growing evidence that most cases of AD likely involve a combination of genetic and environmental risk factors. Identifying and validating these risk factors remains one of the most critical scientific challenges in order to find novel therapeutic targets against AD. Genetic and non-genetic risk factors are implicated in the pathophysiology of sporadic AD (Fotuhi et al., 2009). At present, APOEε4 is the only validated genetic risk factor for sporadic AD (Qiu et al., 2009). Various not-genetic risk factors are implicated in the pathophysiology of sporadic AD. In particular, several diseases contribute to enhance the risk of developing AD. Indeed, brain trauma, cardiovascular diseases, carotid atherosclerosis, history of hypertension or high cholesterol, Type II diabetes, stroke or transient ischemic attack are considered risk factors for AD. However, the molecular mechanisms by which these non-genetic risk factors may modify cognitive function have not yet been elucidated. Notably, the Receptor for Advanced Glycation Endproducts (RAGE) is implicated in the pathogenesis of these not-genetic risk for AD and also in the progression of AD (Perrone et al., 2012). RAGE is a multiligand receptor of the immunoglobulin superfamily of cell surface molecules acting as counter-receptor for various ligands, such as AGEs, S100/calgranulins family of pro-inflammatory proteins, HMGB1, Aβ peptides, and the family of beta-sheet fibrils (Bierhaus et al., 2005; Bierhaus and Nawroth, 2009). RAGE ectodomain is constituted by one V-type domain followed by two C-type domains. The N-terminal V-domain is implicated in the recognition of RAGE ligands (Yan et al., 2000). Studies with RAGE −/− mice confirmed that RAGE contributes to AD (Schmidt et al., 2009; Yan et al., 2009a, 2012). Some evidence indicates that RAGE induces neurodegeneration in AD via multiple pathways. In AD brain, RAGE is over-expressed in neurons, microglia, astrocytes, and in brain endothelial cells (Yan et al., 2000; Deane et al., 2009). The activation of RAGE in neuronal cells promotes synaptic dysfunction. RAGE triggering in glial cells also leads to neurodegeneration by inducing inflammation. Moreover, RAGE is responsible for the transport of Aβ from the blood to the brain (Deane et al., 2003), inducing cerebrovascular dysfunction that ultimately results in neurovascular inflammation and subsequent synaptotoxicity (Deane and Zlokovic, 2007). In addition, the G82S RAGE allele (a polymorphism in RAGE sequence) is associated with increased risk of AD (Daborg et al., 2010), supporting the hypothesis that RAGE is implicated in the progression of sporadic AD. It is interesting to note that RAGE activation leads to a positive feed-back loop, which leads to enhanced RAGE expression promoting a chronic effect of RAGE function (Bierhaus et al., 2005; Perrone et al., 2012). In agreement, it has been shown that RAGE amplifies Aβ effects at the early stages of AD, when the level Aβ is low, ultimately leading to neuronal dysfunction and neurodegeneration (Perrone et al., 2012). In the light of the capability of RAGE to induce a positive feedback loop and because it is implicated in the pathogenesis of several diseases that are risk factors for AD, RAGE seems to represent an excellent mediator of the effect of diseases known to promote AD, and it is a therapeutic target to prevent AD. Supporting this hypothesis, it has been shown that several RAGE ligands that are implicated in AD pathogenesis play a key role and are prognostic markers for diseases that constitute a risk for AD. S100A1 is implicated in hypertension (Kraus et al., 2009). S100A9 is a marker of cardiovascular diseases (Cotoi et al., 2014). S100A12 is elevated in atherosclerosis (Abbas et al., 2012). Advanced Glycation Endoproducts (AGEs) participate in the pathophysiology of diabetes (Bierhaus et al., 2005). HMGB1 is implicated in cerebral ischemia (Xiong et al., 2014). S100B is a prognostic marker for brain trauma (Mercier et al., 2013).

In the present review, we will summarize the evidence supporting the role of hypertension, cardiovascular diseases, diabetes, cerebral ischemia, and brain trauma as risk factors for AD, as well as the data supporting the key role of RAGE in the pathophysiology of these diseases. We will also discuss the data supporting the hypothesis that risk factors for AD induce the triggering of RAGE, which is the key molecular event that initiates a chronic positive feedback loop, ultimately leading to AD etiology.

In the last years the relevance of the inflammatory process and early microglia activation in AD progression has been shown. Indeed, all the risk factors for AD induce inflammation. For this reason, we will also discuss the role of RAGE in microglia activation as a molecular mechanism implicated in AD progression.

Hypertension and AD

It has been shown that cognition is closely related to cerebrovascular function (Iadecola et al., 2009; Dickstein et al., 2010). Several epidemiological studies have been carried out in order to investigate the correlation between cerebrovascular dysfunction and dementia. In one study, it has been observed that patients who finally developed dementia were characterized by an increase in blood pressure from mid-life through to late-life, compared to those who did not develop dementia (Stewart et al., 2009). It has also been demonstrated that hypertension leads to an increase in white matter lesions (Firbank et al., 2007). Various investigations showed that mid-life hypertension is a risk factor for the development of AD (Launer et al., 2000; Kivipelto et al., 2001; Skoog et al., 2005; Takeda et al., 2008). Since hypertension induces cerebrovascular necrosis and arteriosclerosis, it has been proposed that

anti-hypertensive treatments may prevent or ameliorate cognitive dysfunction (Peters et al., 2008, 2009; Takeda et al., 2008; Valenzuela et al., 2012). In agreement, a randomized controlled study demonstrated that elderly hypertensive patients treated with antihypertensive medication showed a decreased risk not only for vascular dementia, but also for AD (Forette et al., 2002). Several studies investigated the neuropathological processes that link hypertension to AD, with a particular regard to the white brain white mater alterations (Valenzuela et al., 2012). Hypertension induces brain microvascular disease, inflammation and blood-brain barrier breakdown (Pantoni and Garcia, 1995; Englund, 2002; Fernando et al., 2006). These alterations of the white matter strongly correlate with the development of severe cognitive decline and predict the progression from mild cognitive impairment to AD dementia over 3 years (van Straaten et al., 2008).

Role of RAGE in hypertension as risk factor for AD

Although epidemiological investigations indicate that hypertension is a strong predisposition factor for AD, the mechanistic explanation is still controversial. However, several data strongly support the hypothesis that hypertension is characterized by RAGE activation, which in turn promotes AD progression.

Alterations in the vascular system play an integral role during AD. It has been shown that systemic circulatory changes actively contribute to both the onset and progression of AD (Bell, 2012). A pathological feature of AD, underlying the cognitive impairment and dementia, is the accumulation of Aβ in the brain, and increasing evidence points out a central role for Aβ transport across the Blood Brain Barrier (BBB) in determining central nervous system concentrations of Aβ, because peripheral Aβ interacts with the cerebral vasculature and influences its own deposition in brain (Perrone et al., 2012). The BBB maintains the right balance of the intracerebral pool of Aβ with that of the bloodstream (Perrone et al., 2012). RAGE contributes to the physiological entrance and efflux of Aβ in and out of the brain (Perrone et al., 2012). BBB dysfunction is associated to both hypertension and AD (Qiu et al., 2009; Perrone et al., 2012). The role of RAGE in promoting BBB dysfunction in AD is well characterized (Perrone et al., 2012). RAGE is upregulated in AD brain vasculature (Yan et al., 1996; Takeda et al., 2010; Valente et al., 2010). The transport of Aβ is strongly impaired and undetectable in RAGE null mice (Deane et al., 2003). RAGE-mediated transport of Aβ leads to neurovascular stress, induction of the expression of TNF-α and IL-6, which are detected mostly at the level of neurons. Infusion with physiological concentration of Aβ (50 pM) does not induce the expression of proinflammatory cytokines, while neurovascular inflammation is detected when pathological concentrations of Aβ (4.5 nM) are infused in the mice (Deane et al., 2003). Infusion of anti-RAGE IgG ameliorates vascular dysfunction and blocks endothelin-1 expression in the Tg2576 AD mice model (Deane et al., 2003).

Hypertension is also associated to RAGE activation, which in turn promotes vascular dysfunction (Kikuchi et al., 2013). Hypertension induces RAGE upregulation in brain vessels of the cortex and hippocampus in mice (Carnevale et al., 2012). Epidemiological studies suggest that antihypertensive treatments using Angiotensin receptor blockers (ARBs) reduce the activation of RAGE (Kikuchi et al., 2013). It has been shown that the ARB telmisartan significantly down-regulates serum HMGB1 levels in autosomal dominant polycystic kidney disease patients with hypertension (Nakamura et al., 2012). These findings suggest that treatment with ARBs blocks RAGE activation by inhibiting the expression of the RAGE ligand HMGB1.

A recent study clearly indicates that hypertension promotes AD by activating RAGE and that inhibition of RAGE abolishes hypertension–induced AD phenotype, strongly suggesting that RAGE is the key molecule that transduces the effect of hypertension as a risk factor for AD (Carnevale et al., 2012). This study demonstrates that a mouse model of hypertension shows AD alterations, such as amyloid plaques, neuroinflammation, BBB dysfunction, and cognitive impairment (Carnevale et al., 2012). In this mouse model, hypertension induces RAGE upregulation in the brain vessels of the cortex and hippocampus. Notably, in this mouse model, RAGE inhibition completely blocks hypertension-induced AD phenotype and rescues the cognitive impairment and parenchymal Aβ deposition (Carnevale et al., 2012). Interestingly, this study underlines the role of vascular dysfunction in promoting AD by demonstrating that a mouse model of hypertension develops an AD phenotype. Notably, this mouse model does not carry any transgene associated to familiar AD. In addition, this study clearly underlines the key role of RAGE in promoting AD etiology (Fig. 1).

Cardiovascular diseases and AD

The vascular endothelium, which regulates the passage of macromolecules and circulating cells from blood to tissue, is a major target of oxidative stress, playing a key role in the pathophysiology of vascular diseases. Since the vascular endothelium, neurons and glia are all able to synthesize, store and release reactive oxygen species (ROS) and vascular active substances in response to certain stimuli, their contribution to the pathophysiology of AD can be very important. Several studies suggest that sporadic late onset AD is a consequence of vascular dysfunction, where ROS accumulation ultimately leads to AD neurovascular dysfunction (Perrone et al., 2012). In agreement, recent large-scale genome-wide association studies clearly highlighted the involvement of cardiovascular disease-induced pathways in AD (Liu et al., 2014). Atherosclerosis affects the vascular structure and

function promoting neurodegenerative processes, which ultimately participate in AD. Cardiovascular diseases lead to vascular pathology involving arterial stiffness, arteriolosclerosis, endothelial degeneration and blood-brain barrier dysfunction, which produce chronic cerebral hypoperfusion. Several studies indicate that cardiovascular diseases promote cerebral hypoperfusion, which ultimately initiates AD pathology, characterized by selective brain atrophy, white matter changes and accumulation of abnormal proteins such as Aβ (Kalaria et al., 2012).

Role of RAGE in cardiovascular diseases as a risk factor for AD

Advanced glycation endproducts (AGEs) are a group of modified molecular species formed by nonenzymatic reactions between the aldehydic group of reducing sugars with proteins, lipids, or nucleic acids (Bierhaus et al., 1998). Formation and accumulation of AGEs is related to the aging process and is accelerated in diabetes (Bierhaus et al., 1998, 2001; Bierhaus and Nawroth, 2005). AGEs are generated in hyperglycemia, but their production also occurs in settings characterized by oxidative stress and inflammation (Bierhaus et al., 1998, 2001, 2008; Bierhaus and Nawroth, 2009). These species promote vascular damage and acceleration of atherosclerotic plaque progression mainly through two mechanisms: directly, altering the functional properties of vessel wall extracellular matrix molecules, or indirectly, through activation of cell receptor-dependent signaling (Bierhaus et al., 1998, 2008; Bierhaus and Nawroth, 2009). Interaction between AGEs and their receptor for RAGE, which is present in all cells relevant to atherosclerosis, alters cellular function, promotes gene expression, and enhances the release of pro-inflammatory molecules (Bierhaus et al., 1998, 2008; Bierhaus and Nawroth, 2009). Several studies including our own underlined the importance of the RAGE interaction and downstream pathways, leading to vessel wall injury (Bierhaus et al., 1998, 2001, 2005, 2008; Perrone et al., 2009, 2012; Yan et al., 2009b). Various studies indicate that inhibition of RAGE may be essential in controlling and preventing cardiovascular complications (Yan et al., 2009b). In the light of the role of cardiovascular diseases as risk factors for AD and the role of RAGE in the pathogenesis of cardiovascular diseases, it is possible to hypothesize that RAGE is the molecular link that transduces the effect of cardiovascular diseases in promoting AD onset and

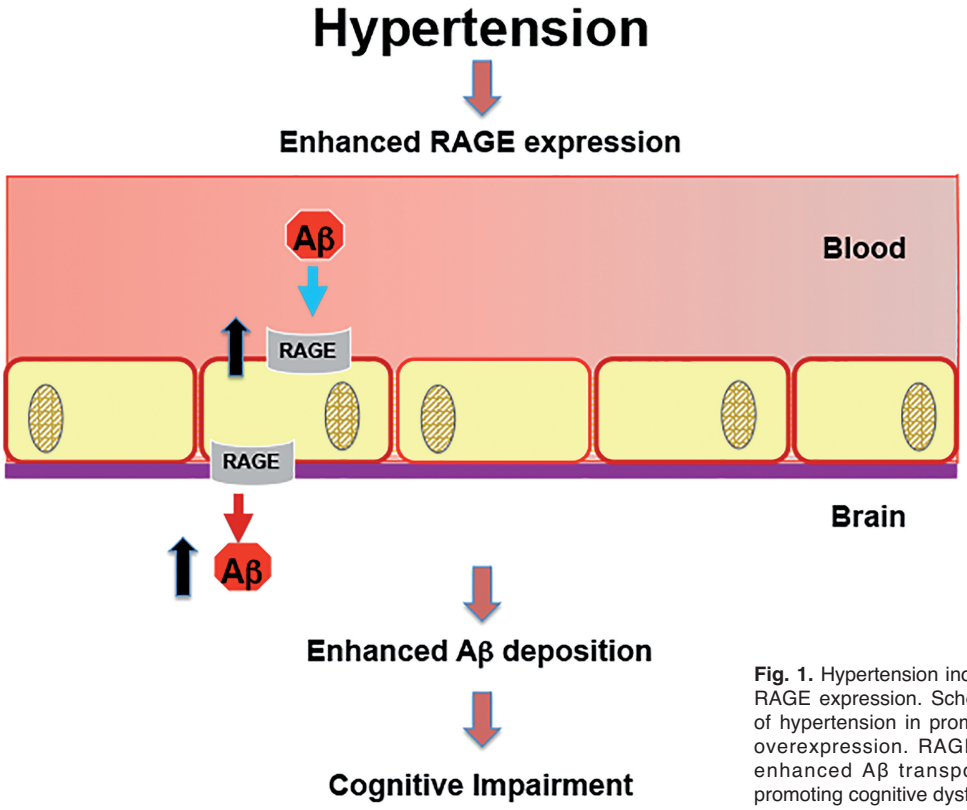

Fig. 1. Hypertension induces an AD-like phenotype by promoting RAGE expression. Schematic representation illustrating the role of hypertension in promoting AD phenotype by inducing RAGE overexpression. RAGE overexpression at the BBB leads to enhanced Aβ transport into the brain and Aβ deposition, promoting cognitive dysfunction.

progression.

Diabetes and AD

Several research groups demonstrated an association between diabetes and AD. Diabetes and AD are characterized by similar clinical symptoms and signs, such as cognitive dysfunction, impaired fasting glucose, chronic hyperglycemia, hippocampal atrophy. Diabetic patients show a high risk of cognitive impairment, which may result from chronic hyperglycemia, repeated occurrences of severe hypoglycemia, microvascular complications, and insulin resistance occurring during the disease (Chen and Zhong, 2013). Thus, diabetes has an impact on the patients' brain function. Some studies demonstrated that diabetic patients show an enhanced probability to develop AD (Vignini et al., 2013), even if it is still controversial whether diabetes enhances the risk for sporadic AD. Diabetes is mostly associated to vascular dementia and its role in promoting cognitive impairment in AD is still debated (Luchsinger, 2012). The most accredited hypothesis is that diabetes is a risk factor for AD by promoting cerebrovascular dysfunction (Luchsinger, 2012). Interestingly, a recent study demonstrated that the expression of the diabetes-related gene is altered in AD patients as well as in the 3Tg AD mice model, supporting the hypothesis that there is a cross-talk between these 2 diseases and they share common pathways (Hokama et al., 2014). Indeed, AD is also defined as type 3 diabetes, because AD brains show lower levels of insulin and Insulin-like Growth Factor (IGF), implicating insulin resistance in AD neuropathology (Steen et al., 2005; Craft, 2012). Mechanisms analogous to those accounting for peripheral insulin resistance in type-2 diabetes likely underlie impaired brain insulin signaling in AD. In agreement, recent findings demonstrate that Aβ oligomers trigger pathogenic mechanisms in AD brain, which are similar to mechanisms present in diabetes (Ma et al., 2009; Bomfim et al., 2012; Craft, 2012). Notably, an anti-diabetic agent is protective of Aβ-induced impaired insulin signaling in AD brain (Bomfim et al., 2012). It has been detailed that Aβ oligomers bound to hippocampal neurons trigger the removal of the insulin receptors (IRs) from the plasma membrane, resulting in impaired insulin signaling (Zhao et al., 2008; De Felice et al., 2009). Several studies including our own indicate that Aβ oligomers are the most toxic species (Lesné et al., 2006; Lesné et al., 2008; Selkoe, 2008; Mazarguil et al., 2012). Interestingly, we also reported that oligomers are associated to the postsynapse in AD hippocampi, while they are absent at the postsynapse in cognitively intact elderly individuals whose brains presented amyloid deposits (Bjorklund et al., 2012). These data suggest that in AD brain may act some co-factors or altered signaling pathways that are necessary for the interaction of Aβ oligomers with the postsynapse. These results further confirm that there is a correlation between altered insulin signaling and Aβ toxicity. In agreement, several studies indicate that insulin improves learning and memory and modulates Aβ in AD (Benedict et al., 2004; Reger et al., 2008; Craft et al., 2012; Freiherr et al., 2013). Indeed, it has been hypothesized that there is cross-talk between brain and peripheral tissues, which plays a key role in triggering the onset of sporadic AD (De Felice, 2013).

Diabetes and AD are both characterized by enhanced oxidative stress (Perrone et al., 2012; De Felice, 2013). The transient production of Reactive Oxygen Species (ROS) in the brain is implicated in synaptic signaling (Serrano and Klann, 2004). In addition, it seems that moderate ROS levels increase peripheral insulin sensitivity (Cheng et al., 2010). On the other hand, the imbalance between mitochondrial ROS production and the levels of intracellular antioxidant defenses produces mitochondrial dysfunction, increased ROS levels leading to oxidative stress, which participates in both peripheral insulin resistance and AD (Reddy et al., 2009; Cheng et al., 2010). Interestingly, Aβ oligomer–induced neuronal oxidative stress (De Felice et al., 2007; Perrone et al., 2010; Mazarguil et al., 2012; Saraiva et al., 2012) is blocked by insulin (De Felice et al., 2009; Picone et al., 2011), further confirming the relevance of insulin resistance in AD and that common pathways are activated in diabetes and AD.

Diabetes and sporadic AD are both characterized also by the toxic effects induced by the Advanced Glycation Endproducts (AGEs) (Perrone et al., 2012). AGEs are considered important markers of oxidative stress and they accumulate during aging and diseases. AGEs are markers of carbonyl stress and accumulate following an increased level of sugars and reactive dicarbonyl compounds such as glucose, fructose, deoxyglucose, glyoxal, methylglyoxal, and triose-phosphates (Fleming et al., 2011). AGEs derive from a multistep reaction of reducing sugars or dicarbonyl compounds with the amino groups of proteins (Rahmadi et al., 2011). The irreversible formation of AGEs results in protease resistant cross-linking of peptides, proteins, and other macromolecules. AGEs are localized in pyramidal neurons that appear to selectively accumulate AGEs in an age-dependent manner. In the AD brain, AGEs colocalize with activated astrocytes (Horie et al., 1997). The percentage of AGE positive neurons and astroglia increase in Alzheimer with the progression of disease, which might contribute to many aspects of neuronal dysfunction in AD by processes such as inflammatory activation of microglia, or direct cytotoxicity via formation of free radicals (Srikanth et al., 2011), presumably mediated through activation of their receptor RAGE (Srikanth et al., 2011). AGEs are known to be involved in the traditional microvascular complications of type-2 diabetes (Stitt, 2001; Schalkwijk et al., 2002; Sullivan and Feldman, 2005). AGEs accumulate in AD brain and accelerate Aβ deposition (Loske et al., 2000; Vitek et al., 1994), participating in AD progression. Indeed, it has been shown that induction of diabetes in a transgenic AD mouse model

results in AGEs production, which in turn is responsible for increased amyloid plaque deposition (Wang et al., 2014), demonstrating that diabetes promotes AD pathogenesis.

Role of RAGE in diabetes as risk factor for AD

Diabetic AD patients show enhanced cell damage, which is RAGE dependent (Valente et al., 2010). Indeed, type-2 diabetes is characterized by enhanced production of AGEs and increased RAGE expression. Thus, AGEs and RAGE seem to mediate the synergistic effect of diabetes and AD in producing neurovascular dysfunction (Perrone et al., 2012). In support of this hypothesis, in the brain of a rat model of diabetes, activation of RAGE with AGEs leads to NF-κB dependent expression of BACE1 (Guglielmotto et al., 2010), a key enzyme implicated in the production of Aβ. In addition, overexpression of RAGE anticipates the onset of neuronal dysfunction in double transgenic mice overexpressing neuronal mAPP and RAGE (Tg mAPP/RAGE) compared to the single Tg expressing mAPP only (Arancio et al., 2004). RAGE-dependent anticipation of neuronal dysfunction was demonstrated by earlier impairment of learning/memory in double Tgs mAPP/RAGE compared to single Tg mAPP mice. Exacerbation of memory impairment correlates with an anticipation of synaptic dysfunction in the hippocampus of double Tgs as demonstrated by alteration of LTP (Arancio et al., 2004). A decreased number of cholinergic fibers and presynaptic terminals appears earlier in mAPP/RAGE compared to mAPP mice (Arancio et al., 2004). On the contrary, inhibition of RAGE confers a neuroprotective effect in AD mice, as demonstrated in double Tg mice expressing mAPP and a dominant negative form of RAGE (DNRAGE) in neurons (Arancio et al., 2004). DNRAGE encodes for a truncated form of RAGE lacking the intracellular domain necessary to induce RAGE-mediated signaling, while maintaining the extracellular domain for ligand binding. DNRAGE expression blocks the function of endogenous RAGE (Arancio et al., 2004). Double Tg mAPP/DNRAGE performed better in learning and memory test compared to single Tg mAPP. Expression of DNRAGE completely prevented neuropathologic changes such as loss of cholinergic fibers induced by mAPP (Arancio et al., 2004).

Studies in animal models of AD confirmed that diabetes participates and promotes AD pathophysiology. Indeed, induction of diabetes in a rabbit non transgenic mouse model produces an AD-like phenotype (Bitel et al., 2012). In these rabbits, diabetes induces tau hyperphosphorylation, the formation of Aβ oligomers in the hippocampal brain parenchima and surrounding vasculature, and enhanced RAGE expression, which co-localizes with Aβ deposits (Bitel et al., 2012),

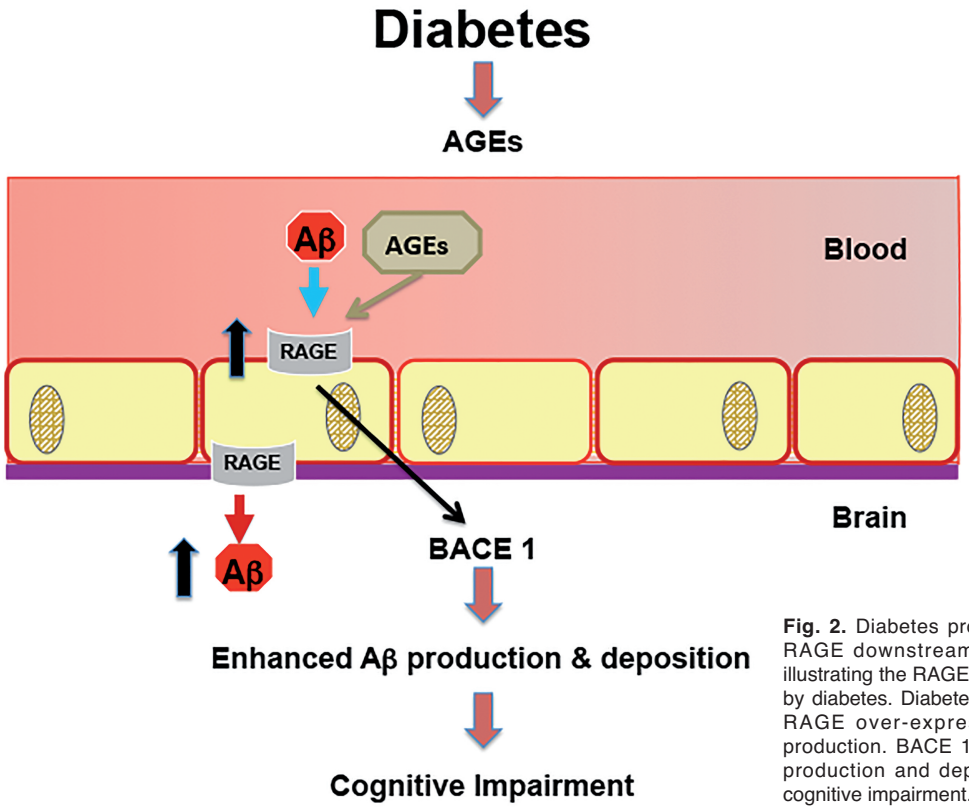

Fig. 2. Diabetes promotes AD progression bv activating a RAGE downstream pathway. Schematic representation illustrating the RAGE-dependent downstream pathway induced by diabetes. Diabetes leads to AGEs formation, which induce RAGE over-expression leading to enhanced BACE 1 production. BACE 1 overexpression leads to increased Ab production and deposition into the brain, participating in cognitive impairment.

suggesting that RAGE may be implicated in AD-like phenotype. Confirming the hypothesis that RAGE mediates the effects of diabetes in AD pathogenesis, it has been shown that diabetes-induction in an AD Tg mice model anticipates and increases Aβ deposition, which parallels RAGE over-expression (Wang et al., 2014) (Fig. 2).

Recent evidence strongly indicates that AD is an age-related metabolic neurodegenerative disease, which presents an impaired glucose metabolism as an invariant feature. Alteration of glucose metabolism in AD precedes cognitive dysfunction (Cunnane et al., 2011). Glucose transport into the brain of AD patients is impaired due to insulin resistance (Chen and Zhong, 2013). Brain insulin resistance and subsequent glucose hypometabolism negatively impact cognitive functions, participating in the pathophysiology of AD (Chen and Zhong, 2013). AD is also associated with cerebrovascular amyloid angiopathy, whose pathogenesis is strongly related to RAGE activation (Sato et al., 2011). It has been recently hypothesized that RAGE and vascular dysfunction related to cerebrovascular amyloid angiopathy participate in affecting the insulin pathway in AD (Sato et al., 2011). Thus, RAGE is believed to mediate the effect of diabetes in producing metabolic dysfunction and insulin resistance in AD. In agreement with this hypothesis, we and others demonstrated that RAGE triggering induces the expression of Thioredoxin Interacting Protein (TXNIP) (Perrone et al., 2009; Sbai et al., 2010; Zitman-Gal et al., 2010; Perrone et al., 2012; Zitman-Gal et al., 2012). TXNIP was initially characterized for its capability to inhibit thioredoxin, leading to oxidative stress (Turturro et al., 2007; Perrone et al., 2009). However, recent studies demonstrated that TXNIP regulates both systemic and cellular glucose metabolism (Muoio, 2007; Parikh et al., 2007; Blouet and Schwartz, 2011; Blouet et al., 2012; Hand et al., 2013), and its expression is associated to the senescence process (Mousa et al., 2009). TXNIP modulates glucose uptake by regulating the endocytosis of the glucose transporter GLUT 1 (Wu et al., 2013). Notably, TXNIP plays a central role in inducing insulin resistance. Indeed, TXNIP KO mice are resistant to diabetes induction (Chutkow et al., 2010). Thus, TXNIP is an intriguing candidate molecule that may provide a common link between brain insulin resistance and AD. In agreement, we demonstrated that TXNIP is early over-expressed in the hippocampus of the 5xFAD AD mice model (Perrone et al., 2012). Our results also strongly support the hypothesis that the RAGE-TXNIP axis may be the molecular pathway that mediates the effects of diabetes as a risk for AD (Perrone et al., 2012), by promoting neurovascular inflammation and contributing to brain insulin resistance.

Cerebral ischemia and AD

Clinical data revealed a synergistic risk between stroke and AD dementia. Stroke increases the risk of developing AD dementia by a factor of three (Kalaria, 2000). In addition, the occurrence of stroke during a given stage of AD pathology increases eight fold the risk of developing dementia in AD patients (Snowdon et al., 1997) and exacerbates cognitive impairment in AD animal models (Li et al., 2011).

Notably, cerebral ischemia enhances Aβ production, as observed in human hippocampus (Qi et al., 2007) and in the hippocampus of animal models of stroke (Popa-Wagner et al., 1998; Li et al., 2010). Cerebral ischemia modulates the entire amyloidogenic cascade. Animal models of brain ischemic injury show enhanced amyloid precursor protein (APP) (Hall et al., 1995) and BACE 1 (Wen et al., 2004; Sun et al., 2006) expression. Postmortem tissue from individuals with AD dementia present senile plaques more likely situated near microhemorrhages and broken capillaries (Cullen et al., 2006). In the APP23 transgenic AD mouse, chronic hypoxia leads to enhanced BACE 1 expression and Aβ production as well as aggravating cognitive impairment (Sun et al., 2006). Several studies suggest that the production of β-amyloid peptide after ischemia as well as ischemia independently induce oxidative stress, which in turn, increase β- and γ-secretase activities, which further enhance β-amyloid peptide production. Indeed, there are many molecular and pathophysiolocic mechanisms that are common in ischemic brain disorders and AD, such as the presence of neuritic plaques, tangles, inflammation, massive neuronal death, and dementia in ischemic brain (Pluta et al., 2013). Moreover, it has been shown that both stroke and AD are preceded by a significant reduction of brain blood flow (De la Torre, 2005).

Brain ischemia is followed by a massive production of free radicals, in particular during reperfusion, leading to oxidative stress (Pluta et al., 2013). Oxidative stress further enhances Aβ deposition (Pluta et al., 2013). Indeed, stroke leads to enhanced β- and γ-secretase-mediated APP processing, which increase Aβ production and deposition (Pluta et al., 2013). Aβ oligomers are the most toxic species (Lesné et al., 2006, 2008; Selkoe, 2008; Mazarguil et al., 2012) and their formation after brain ischemia produces various events that are common to AD pathology, such as hyperphosphorylation of tau protein and altered function of neurons, microglia and oligodendrocytes (Pluta et al., 2013). These data support the hypothesis that stroke-induced Aβ production and oxidative stress are implicated in sporadic AD etiology.

Role of RAGE in cerebral ischemia as a risk factor for AD

RAGE is highly implicated in brain ischemia pathophysiology. Stroke-induced Aβ production activates RAGE, which induces neurodegeneration directly when activated in neuronal cells, or indirectly when it activates the microglia (Pluta et al., 2013). RAGE expression is enhanced in brain vasculature and glial cells after stroke (Kamide et al., 2012). Brain

ischemia leads to neuronal apoptosis in the CA1 region of the hippocampus (Kamide et al., 2012), strongly suggesting that stroke contributes to sporadic AD pathology, since neurodegeneration in the CA1 region is implicated in AD. Notably, RAGE KO mice show a significant reduction of neuronal death in the CA1 region following cerebral ischemia (Kamide et al., 2012), as well presenting reduced inflammation and vascular injury (Kamide et al., 2012). Another study revealed a direct role of neuronal RAGE in promoting stroke-induced neurodegeneration. Mice expressing a dominant negative form of RAGE (DNRAGE) showed decreased stroke volume, indicating that RAGE signaling is directly implicated in cerebral ischemia pathology (Hassid et al., 2009). These studies indicate that RAGE may mediate at least in part the effect of stroke as a risk factor for AD.

The activation of the innate immunity (macrophages and microglia) plays a role in both stroke and AD progression. Brain ischemia is also characterized by hypoxia. Interestingly, hypoxia induces the activation of RAGE in macrophages (Xu et al., 2010), suggesting that RAGE may be implicated also in the activation of the innate immunity. In agreement, the role of RAGE and its ligand HMGB1 in ischemic brain damage due to infiltrating macrophages has been demonstrated (Muhammad et al., 2008). The function of RAGE in promoting macrophage infiltration was investigated by generating chimeric mice, in which RAGE (-/-) bone marrow cells were transplanted into wild-type mice. RAGE deficiency in bone marrow-derived cells resulted in reduced infarct size (Muhammad et al., 2008).

Brain trauma and AD

A recent epidemiological study revealed that after brain injury, individuals with mild cognitive impairment (MCI) showed higher Aβ deposition and neuro-degeneration compared to head trauma affected patients who were cognitively normal (Mielke et al., 2014), suggesting that brain trauma is a risk for AD by promoting Aβ production and neurodegeneration.

Giunta and colleagues recently described in a review the relevance of traumatic brain injury (TBI) in promoting sporadic AD (Giunta et al., 2012). This review highlights the role of microglia activation in promoting AD pathology as a long term consequence of brain injury (Giunta et al., 2012). The persistence of microglia activation after TBI has been described by epidemiological studies and in animal models of TBI (Breunig et al., 2013).

Several AD-characteristic alterations occur following TBI. They include neuronal and synaptic loss (Maxwell et al., 2010), enhanced Aβ deposition, tau hyperphosphorylation and gliosis (Breunig et al., 2013). In addition, several animal models and epidemiological studies demonstrated that TBI is implicated in AD progression (Breunig et al., 2013). TBI is also characterized by enhanced oxidative stress and hypoxia, which in turn promote brain inflammation (Breunig et al., 2013) and contribute to enhance Aβ deposition as we described above.

Role of RAGE in brain trauma as a risk factor for AD

RAGE and its ligand HMGB1 are over-expressed in TBI patients, suggesting the role of the inflammatory reaction in the consequences of TBI (Gao et al., 2012) and that RAGE may be implicated in mediating the effects of TBI as a risk factor for AD. However, up to now there are no studies directly demonstrating the role of RAGE in promoting AD pathology after TBI.

Inflammation, microglia activation and AD

Some evidence underlines the relevance of inflammation in AD progression (Sastre et al., 2011). Inflammatory mediators are detected before amyloid plaque and tangle formation (Sastre et al., 2011). In agreement, the majority of the diseases that represent a risk factor of AD are characterized by enhanced inflammation (Sastre et al., 2011). For this reason, several studies investigated the role of the innate immunity in AD progression (Sastre et al., 2011).

The CNS possesses an immunological capacity that differs from most peripheral tissues relying on astrocytes and specialized innate cells, including microglia and macrophages.

Microglia are the resident macrophage population of the central nervous system (CNS) (Nayak et al., 2014). Adequate microglial function is crucial for a healthy CNS. Microglia are not only the first immune sentinels of infection, contributing to both innate and adaptive immune responses locally, but are also involved in the maintenance of brain homeostasis (Ginhoux et al., 2013). Microglia in normal brain are sentinel cells, which become reactive in AD (Raivich, 2005). They actually surrounds degenerating cells, clear cellular debris, and predominate around Aβ plaques (Fetler and Amigorena, 2005). Microglia proliferates around neurons prior to their neurodegenerative process in murine models of AD (Fuhrmann et al., 2010). It has been shown that an increase of activated microglia parallels cognitive impairment (Edison et al., 2008). However the relationship between activated microglia and AD progression is still a matter of debate. Indeed, recent studies were not able to confirm the potential link between neuroinflammatory histopathology and the severity of neurofibrillary degeneration in human brain (Streit et al., 2014). On the other hand, AD is a disease related to aging. Indeed, according to the concept of aging firstly demonstrated in Lopez-Otin, the following physiological processes of microglial cells can be altered in the context of AD. 1) Proliferation; (2) Morphological changes; (3) Migration (4) Intercellular communication; (5) Phagocytosis; and (6) Proteostasis (Mosher and Wyss-Coray, 2014). However, classifying microglial reactivity under aging and AD remains difficult to

demonstrate, because microglia can be differentially activated by signaling factors to adopt protective or harmful phenotypes (Mosser and Edwards, 2008).

Role of RAGE in microglia activation in AD

The function of RAGE in Aβ-mediated neurodegeneration and AD is complex, based on the interaction between Aβ and RAGE and on the coordination between inflammatory signals from neurons and microglia.

RAGE is present in microglia and astrocytes, as well as in neurons and in cells of the blood-brain barrier (endothelial and smooth muscle cells) and its expression levels strongly increase in patients affected by AD and diabetes mellitus (DM) (Donahue et al., 2006; van Straaten et al., 2008).

The increased expression of RAGE in microglia and the significance of microglia in AD, essentially suggest that RAGE and Aβ may be involved in a tiny, but composite loop, in which each component is modulated and in turn modulates the signaling and the activity of the others. Such events, in conclusion, result in sustained generation of toxic mediators and, ultimately, exacerbate neuroinflammation leading to neuronal stress and injury (Fig. 3).

In this regard Aβ binds RAGE and generates oxidant stress, by activating NF-kB and by inducing the expression of macrophage-colony stimulating factor (M-CSF) and of proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β in neuronal cells (Deane et al., 2003). M-CSF released by neurons stimulates c-fms on microglia, with increased expression of the macrophage scavenger receptor (MSR) and apolipoprotein E (apoE) (Yan et al., 1997). In addition, M-CSF-mediated microglial activation enhances inflammatory cell proliferation and migration, as well as cell survival in the presence of toxic levels of Aβ. Relevantly, the levels of M-CSF significantly increase in the Aβ deposit areas around neurons and in the cerebrospinal fluid of patients with AD (Yan et al., 1997). Furthermore, inflammation enhances the processing of APP in astrocytes by inducing BACE1 expression (van Straaten et al., 2008). BACE I promoter contains NF-kB binding site (Bourne et al., 2007), which is in turn activated by RAGE-ligand interaction during inflammation (Paris et al., 2007). Moreover, RAGE ligands (AGE and Aβ) enhance the expression of RAGE itself, leading to a positive loop that induces the expression of RAGE and subsequent oxidative stress and inflammation, which in turn sustain the formation of AGEs and Aβ (Cho et al., 2009).

The role of RAGE in microglia-dependent neuronal perturbation has been demonstrated in Tg mice over expressing mutant human APP in neurons and RAGE in microglia (Fang et al., 2010). These Tg mice show enhanced IL-1β and TNF-α production, increased

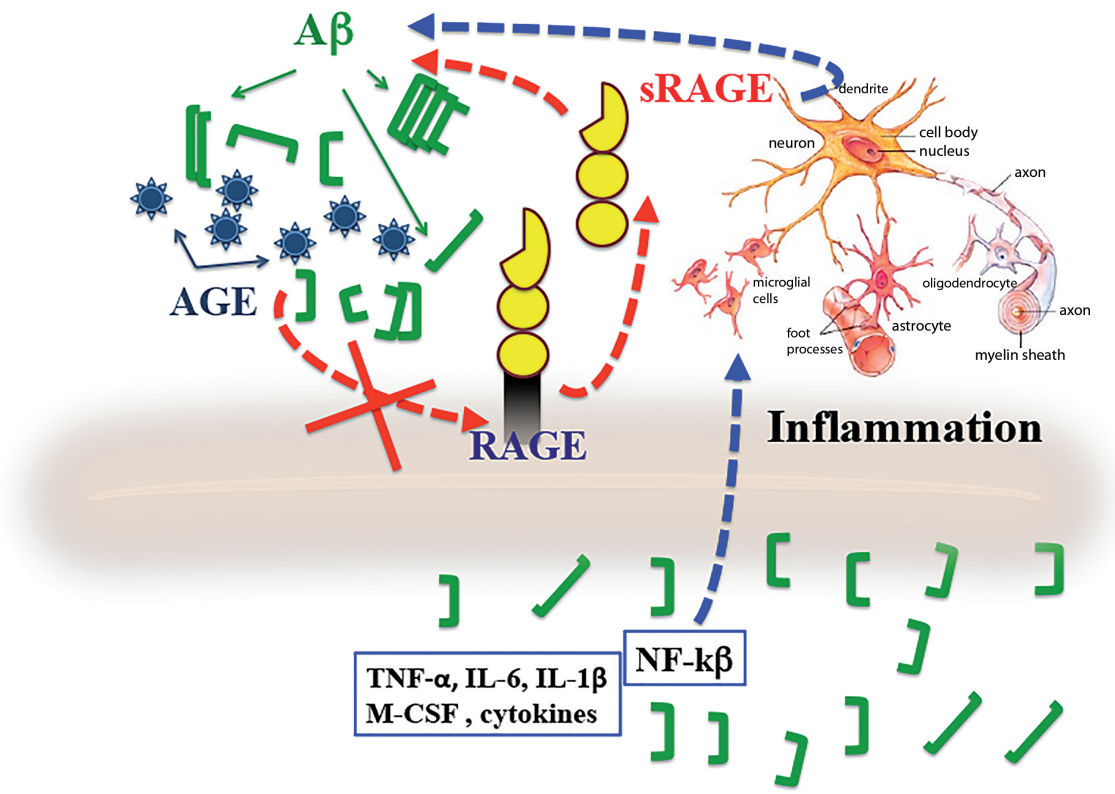

Fig. 3. RAGE-dependent pathways implicated in neurovascular dysfunction in AD. Schematic representation of the role of RAGE in activating a sgnaling cascade implicated in AD progression. We indicate the cross-talk between neuronal cells and glial cells, which ultimately leads to RAGE over activation. RAGE induces a NF-kB-dependent signaling cascade, which promotes the expression of pro-inflammatory factors and further enhances RAGE expression, leading to a positive feedback loop that leads to a chronic inflammation and subsequent neuronal inflammation. We also show the role of sRAGE in inhibiting this chronic signaling cascade.

microglia infiltration, Aβ accumulation, reduced acetylcholine esterase (AChE) activity, and accelerated learning/memory dysfunction (Fang et al., 2010). On the contrary, the expression of a transduction-defective mutant RAGE (DNRAGE) in microglia attenuates Aβ-induced deterioration (Fang et al., 2010), confirming the key role of RAGE in microglia-induced inflammation and the subsequent neuronal dysfunction in AD. In agreement, expression of DNRAGE in microglia inhibits Aβ-induced impairment of long term depression (LTD) in the entorhinal cortex (Origlia et al., 2010).

Differently than RAGE, a protective role has been ascribed to its secreted isoform, sRAGE. sRAGE has the ability to prevent the adverse effects of RAGE signaling by acting as a decoy and controls RAGE-mediated perturbations in microglia and neurons (Emanuele et al., 2005). Accordingly, sRAGE has been used successfully in several animal models to antagonize RAGE-mediated vascular damage (Webster et al., 2012). In addition, sRAGE and Aβ bind together in the periphery forming high molecular weight complexes that are more highly immunogenic and less neurotoxic than Aβ1-42 alone. This last finding might suggest the possibility of using a vaccine targeting both sRAGE and Aβ1-42 to neutralize Aβ deposits in humans (Webster et al., 2012).

Conclusions

Herein, we summarize the studies indicating that RAGE is implicated in the pathogenesis of several diseases that are a risk factor for AD, supporting the hypothesis that RAGE mediates the effects induced by the risk factors for AD, promoting the progression of AD. RAGE participates in sporadic AD pathogenesis by activating several pathways in different cell types, particularly BBB, glia, and neurons.

AD is also defined as Type3 diabetes and is characterized by brain insulin resistance. However, the molecular mechanisms leading to brain insulin resistance in AD are not yet fully elucidated. We demonstrated that RAGE induces the expression of TXNIP (Perrone et al., 2009, 2012; Sbai et al., 2010), which plays a key role in diabetes (Kim et al., 2007), insulin resistance (Xu et al., 2012) and cardiovascular disease (Ferreira et al., 2012). Induction of the RAGE-TXNIP axis can reinforce the role of RAGE as a molecular link between risk factors and sporadic AD progression. Thus, we hypothesize that RAGE mediates the effect of cardiovascular and metabolic diseases by inducing TXNIP expression, leading to neurovascular dysfunction and neurodegeneration in AD (Perrone et al., 2012).

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