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REVIEW ARTICLE

Amyloid-β Production: Major Link Between Oxidative Stress and BACE1

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Abstract Sequential endoproteolytic cleavages operated by the γ-secretase and the β-secretase (BACE1) on the β-amyloid precursor protein result in the production of the β-amyloid (Aβ) species, with two C-terminal variants, at residue 40 or at residue 42. Accumulation in brain tissue of aggregates of Aβ42 is the major pathogenetic event in Alzheimer's disease (AD). The causes of Aβ accumulation in the common sporadic form of AD are not completely understood, but they are likely to include oxidative stress (OS). Data reviewed here shed light on how Aβ generation, oxidative stress, and secretase functions are intimately related in sporadic AD. According to our hypothesis, in sporadic AD, OS resulted from several cellular insults such as aging, hypoxia, hyperglycemia, and hypercholesterolemia—that are well-known risk factors for AD development—can determine a primary induction of γ-secretase and BACE1. The loop proceeds with the generation of Aβ42 and its signaling to BACE1 transcription.

Keywords Alzheimer's disease · BACE1 · Oxidative stress · β-amyloid

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Introduction

Alzheimer's disease (AD) is the most common age-related disease (Bachman et al. 1993); therefore, the risk of AD increases dramatically in individuals above the age of 70 and it is predicted that the incidence of the disease could increase a further 3-fold over the next 50 years. AD can be classified in two forms: sporadic AD, which accounts for the majority of cases, and a rare familial early onset form (FAD), in which gene mutations have been observed.

The β-amyloid peptide (Aβ) is generated following the sequential cleavage of its precursor, the β-amyloid precursor protein (AβPP). AβPP is an integral membrane protein with a single membrane spanning domain, a large, extracellular, N-terminus and a shorter, cytoplasmic, C-terminus. The amyloidogenic processing of AβPP involves two sequential cleavages operated by the β- and the γ-secretases at the N-and C-termini of Aβ sequence, respectively. The β-secretase (BACE1) cleaves AβPP at the beginning of the Aβ sequence, generating an extracellular soluble fragment, called sβAPP, and an intracellular C-terminal named C99. The last fragment is further cleaved by the γ-secretase that produces Aβ peptides of different lengths, these being predominantly Aβ40 and Aβ42.

The central role of Aβ in the pathogenesis of AD is supported by several lines of evidence. Aggregates of Aβ are neurotoxic and initiate a series of events, including the hyperphosphorylation of tau, which results in neuronal cell dysfunction and death (Yankner 1996); moreover, Aβ soluble oligomers have been found to alter memory function in different murine AD models (Dodart et al. 2002; Lesné et al. 2006). All genes bearing mutations that cause FAD, APP, and presenilins 1 and 2, which represent the catalytic core of the γ-secretase, mediate the accumulation

of Aβ42, increasing its production and accumulation (Citron et al. 1992; Citron et al. 1997; Lemere et al.1996).

One of the most well-known and studied effects of Aβ is its capacity to induce, and be induced by, oxidative stress (OS); thus, Aβ induces OS in vivo and in vitro (Hensley et al. 1994; Mark et al. 1997; Murakami et al. 2005; Tabner et al. 2005) and OS is itself able to induce the increased production of Aβ (Paola et al. 2000; Tamagno et al. 2002; Tong et al. 2005).

The cause of modified AβPP processing and Aβ42 accumulation in sporadic AD is unclear but is likely to include OS.

OS increase is believed to be an early event in AD (Nunomura et al. 2001; Cutler et al. 2004) as also confirmed by the extensive oxidative damage observed in mild cognitive impairment (MCI), considered a transition stage between normal aging and dementia (Lovell and Markesbery 2001).

Moreover, the identification of oxidatively membrane damage, cytoskeleton derangement and, consequently, cell death (Perry et al. 2000) suggest that OS plays an important role in AD pathogenesis.

Our studies strengthen the hypothesis that OS may also be a basic common pathway of Aβ accumulation, common to different AD risk factors, such as aging, hypoxia, hyperglycemia, and hypercholesterolemia.

Oxidative Stress in AD

Of note, the major non-genetic risk factor involved in the pathogenesis of sporadic late onset AD is aging, which is strictly related to the damage resulting from reactive oxygen species (ROS) indicative of OS (Markesbery and Carney 1999).

ROS are a by-products of cellular metabolism and are generated during mitochondrial oxidative phosphorylation as molecules with unpaired electrons such as superoxide (O_2^-).

The brain is particularly vulnerable to OS because of its high consumption of oxygen, high levels of polyunsaturated fatty acids, and relatively low levels of antioxidants (Floyd and Hensley 2002). Accumulation of oxidative damage in the brain is particularly dangerous since it is a post-mitotic tissue with neurons exhibiting only a weak self-renewal potential due to their low proliferative capacity.

An increased oxidative burden has been observed in the brain of non-demented elderly and of sporadic AD patients (Behl and Moosmann 2002; Moosmann and Behl 2002).

The free radical hypothesis of aging implies the accumulation of ROS resulting in the damage of the major cell components: nucleus, mitochondrial DNA, membranes, and cytoplasmic proteins (Harman 1992).

Membrane lipids are commonly attacked by ROS, and lipid peroxidation is the most frequently oxidative marker that appears to increase during aging (Zhu et al. 2006). The oxidative modification of membrane fatty acids leads to a structural damage and to the generation of aldehydic end products, such as 4-hydroxynonenal (HNE), which have a high oxidative potential themselves and can impair cellular functions (Keller and Mattson 1998).

Post-mortem analysis of the brains of AD subjects found increased levels of lipid peroxidation in brain regions that are affected by an early neurodegeneration (Mielke and Lyketsos 2006).

Several studies show that also protein oxidation increases with the aging of the brain (Abd El Mohsen et al. 2005) as well as the levels of oxidized proteins in AD patients and this increase strongly correlate with cognitive performance (Keller et al. 2005).

Another well-known age-dependent modification mediated by OS is the DNA oxidative damage. It is well known that mutations in mitochondrial DNA cause a respiratory chain dysfunction that leads to an increase in ROS production. These mitochondrial mutations accumulate during brain aging and neurodegenerative disorders (Corral-Debrinski et al. 1992; Wang et al. 2005).

OS increases with age not only through variations in ROS generation but also in their elimination (Barja 2004). Indirect evidence of cellular OS is the increased expression of molecules involved in oxidant defense, such as heme oxygenase, superoxide dismutases, glutathione transferases, and catalase (Markesbery and Carney 1999); then these neurons do not necessarily succumb to OS, but dynamically regulate their defense mechanisms in response to oxidants.

In the case of neurodegenerative disorders where OS is postulated to play a role, the normal balance between production of and defense against OS has been modified and OS impairs the cellular defences causing a vicious cycle.

These challenges become clear during the AD process, and include a strong presence of increased sulfhydryls, induction of heme oxygenase-1 and increased expression of Cu/Zn superoxide dismutase (Nunomura et al. 1999; Smith et al. 1995; Pappolla et al. 1992), which indicates loss of homeostasis. Moreover, the protein oxidation that increases during aging is strictly associated with the decreased capacity of antioxidant defence machinery (Rodrigues Siqueira et al. 2005).

OS may be an early event in the progression from normal aging to AD pathology. Thus, extensive oxidative damage it has been shown in MCI, a transition stage between normal aging and dementia.

It has been shown that in MCI subjects, plasma levels of non-enzymatic antioxidants and activity of antioxidant

enzymes appeared to be decreased if compared to those of normal aging subjects (Guidi et al. 2006; Sultana et al. 2009). Moreover, levels of oxidative markers appeared to be increased.

Proteomic analysis demonstrated a large number of protein-bound HNE in MCI brain (Song et al. 2009). F2-isoprostanes (F2-IsoPs) levels and neuroprostanes were also significantly increased in MCI patients and in late-stage AD (Markesbery et al. 2005). Moreover, in brains from patients with MCI, acrolein has been found to be elevated in hippocampus and temporal cortex where OS is high. Due to its high reactivity, acrolein is not only a marker of lipid peroxidation but also an initiator of OS by adducting cellular nucleophilic groups found in proteins, lipids, and nucleic acids (Singh et al. 2010). Thus, extensive oxidative damage observed in MCI brain regions suggests that OS may be an early event in progression from normal aging to AD.

Based on these notions, it seems likely that increased production of ROS may act as important mediators of synaptic loss and eventually promote neurofibrillary tangles and senile plaques formation (Kern and Behl 2009).

In summary, the oxidative burden observed in healthy brain aging and in early stages of dementia confirms that the accumulation of oxidatively modified biomolecules is a general hallmark of brain aging and could be an early event in the progression of AD.

Oxidative Stress and Major AD Risk Factors

Our studies, as described below, strengthen the hypothesis that OS may be considered a basic common pathway of AD progression, common to most important AD risk factors.

Hypoxia

It is well known that patients with stroke and cerebral infarction are at risk of AD (Rocchi et al. 2009).

Recent studies have shown that a history of stroke can increase AD prevalence by approximately 2-fold in elderly patients (Schneider et al. 2003; Vermeer et al. 2003). The risk is higher when stroke is concomitant with atherosclerotic vascular risk factor (Jellinger 2002).

Recently it has been proposed that hypoxia can alter APP processing, increasing the activity of the β- and the γ-secretases, resulting in the acceleration of Aβ production and plaques formation in vivo and in vitro (Sun et al. 2006; Zhang et al. 2007).

We recently showed, both in vivo and in vitro, that hypoxia up-regulates BACE1 expression in a biphasic manner, through two distinct mechanisms: (a) an early release of ROS from mitochondria and (b) a late activation of HIF-1α, a molecule that regulates oxygen homeostasis (Guglielmotto et al. 2009). The data suggest that the early post-hypoxic up-regulation of BACE1 depends on the generation of ROS mediated by sudden interruption of the mitochondrial electron transport chain. Although it is generally accepted that intracellular ROS levels change during hypoxia, the direction in which this change occurs is still debated. Many Authors reported that the level of intracellular ROS increases under hypoxia and suggested that mitochondria are the source of ROS involved in this cellular response (Chandel et al. 1998; Turrens 2003; Klimova and Chandel 2008). It is now accepted that hypoxia increases ROS via the mitochondrial transport chain and specifically by the function of complex III (Bell et al. 2007).

Hyperglycemia

Diabetes mellitus, a metabolic disorder characterized by hyperglycemia, is an important risk factor for AD, and multiple mechanisms connecting the two diseases have been proposed.

Hyperglycemia enhances the formation of advanced glycation end-products (AGEs) senescent protein derivatives that result from the auto-oxidation of glucose and fructose (Bucala and Cerami 1992; Brownlee et al. 1988; Takeuchi and Makita 2001).

The involvement of AGEs in brain aging and AD was reported many years ago in studies showing that the microtubule associated protein tau and Aβ were substrates of glycation (Ledesma et al. 1994; Smith et al. 1994; Vitek et al. 1994; Yan et al. 1994; Yan et al. 1995).

More recently it has been reported that AGEs have other pathological effects at cellular and molecular levels. Among these are the production of ROS, especially superoxide and hydrogen peroxide (Carubelli et al. 1995; Muscat et al. 2007). Moreover, glycated proteins increase the rate of free radical production compared to native proteins (Neeper et al. 1992).

Another mechanism through which AGEs mediate the production of OS is the interaction with RAGE, which is a multiligand receptor of the immunoglobulin superfamily of cell surface molecules (Qin et al. 2008). The role of RAGE in the pathogenesis of AD has been extensively studied because it also binds Aβ (Yan et al. 1996).

We recently demonstrated a novel pathogenic mechanism of AGEs, which contributes to Aβ accumulation (Guglielmotto et al. 2010). In streptozotocin rats, as well as in SK-N-BE differentiated neuroblastoma cells, two different AGEs, pentosidine and glyceraldehyde derived pyridinium (GLAP), were able to up-regulate BACE1 expression through their binding with RAGE which is followed by a strong production of ROS and by an activation of the NF-κB pathway, which is a representative

transcription factor activated by RAGE (Granic et al. 2009). Moreover, NF-κB has been recently identified as a molecular intermediate involved in the Aβ-mediated control of BACE1. Thus, the inhibitor of IκB kinase that blocks NF-κB transcriptional activity fully reverses the Aβ42-induced increase of BACE1 promoter transactivation (Buggia-Prevot et al. 2008). These data agree with a previous report showing that BACE1 promoter transactivation could be regulated by NF-κB in neuronal cells (Bourne et al. 2007).

The role of RAGE on BACE1 up-regulation was reported before in RAGE-injected brains of AD animal model and in cultured cells (Cho et al. 2009). Our results confirmed and extended this finding by showing that natural ligands of RAGE, AGEs, mediate BACE1 up-regulation in a diabetic animal model as well as in culture model. Thus, activation of AGEs/RAGE axis, as a result of hyperglycemia, driving the up-regulation of the key enzyme for Aβ production, provides a mechanistic link between diabetes mellitus and AD.

Hypercholesterolemia

Recent studies indicate that alterations in cholesterol metabolism influence some molecular mechanisms involved in AD. Three important lines of evidence have implicated cholesterol in AD; (a) hypercholesterolemia is recognized to be a risk factor for sporadic AD (Puglielli et al. 2003; Panza et al. 2007); (b) epidemiological studies showed that APO-E4 allele is strictly associated with an increased risk of AD (Corder et al. 1993; Evans et al. 2004); (c) feeding cholesterol to rabbits produces some of the pathological hallmarks of AD, including amyloid plaques (Kandiah and Feldman 2009).

Moreover, early epidemiological studies indicated that cholesterol-lowering drugs, belonging to the family of statins, reduce the prevalence of AD (Jick et al. 2000), a conclusion not fully accepted because of other contradictory clinical studies (Kandiah and Feldman 2009; Ishii et al. 2003; Serrano-Pozo et al. 2010).

Thus, if altered cholesterol metabolism in the brain has repeatedly been suggested to be implicated in the pathogenesis of AD, the molecular mechanisms underlying its involvement are still largely unknown.

Cholesterol is essential for normal brain functions; most of it is present in the free form and derives from de novo synthesis by astrocytes, as plasma lipoproteins cannot cross the blood–brain barrier (Puglielli et al. 2003), but cholesterol can only be transformed in oxysterols, cholesterol oxidation products that are important to balance the local synthesis of sterols (Lütjohann et al. 1996). We suggested that oxysterols might represent a link between altered cholesterol metabolism in the brain and AD (Gamba et al. 2011). Thus, we recently demonstrated an enhancement of Aβ binding to neuronal cells exerted by oxysterols relevant in brain physiology such as 27-OH cholesterol, 24-OH cholesterol, and 7β-OH cholesterol. The increase has been related to the strongly oxysterols-mediated up-regulation of CD36 and β1 integrin, a well characterized multireceptor complex, able to stimulate the Aβ binding to neuronal cells.

We have also recently demonstrated an up-regulation of BACE1 mediated by the sterol regulatory element binding protein 2 (SREBP2) transcription factor, that tightly regulates the brain cholesterol metabolism, in rats fed with a high fat diet mimicking cholesterol-rich western diet as well as in differentiated SK-N-BE neuroblastoma cells exposed to high cholesterol levels (Mastrocola et al. 2011).

Since it is well known that BACE1 activity located in cholesterol-rich rafts may be positively modulated by cholesterol levels (Cordy et al. 2003; Wolozin 2004), our data on the direct regulation of BACE1 by SREBP2 transcriptional activity adds new insights on the complex molecular mechanisms underlying the implication of cholesterol in the pathogenesis of AD.

The data here reported strongly supported the hypothesis that OS could be a basic common pathway of Aβ accumulation, as determined by different age-related risk factors (Fig. 1).

Aβ Production is a Major Link Between Oxidative Stress and Pathogenesis of AD

According to the amyloid cascade hypothesis of AD, Aβ is considered to be the primary motor of neuronal degeneration, although the pathway leading to neuronal death is extremely complicated (Hardy and Allsop 1991).

It is still controversial whether the most deleterious form of Aβ peptides in the early stage of AD is represented by the fibrillar or the soluble oligomeric peptide form (Drouet et al. 2000).

Although neuronal degeneration occurs in proximity of the amyloid plaques, some studies have suggested that intermediate Aβ aggregates such as protofibrils or simple oligomers are also involved in AD pathogenesis and even appear to be the most dangerous species (Gong et al. 2003; Kayed et al. 2003; Resende et al. 2008; Tamagno et al. 2006). These data may help to explain, for example, why neurodegeneration and specific spatial learning deficits may occur in AD animal models before the appearance of amyloid plaques (Chui et al. 1999; Koistinaho et al. 2001).

More attention has thus been focused on the early stages of amyloid production and on its maturation from small soluble molecules to oligomers and fibrils with high molecular weight.

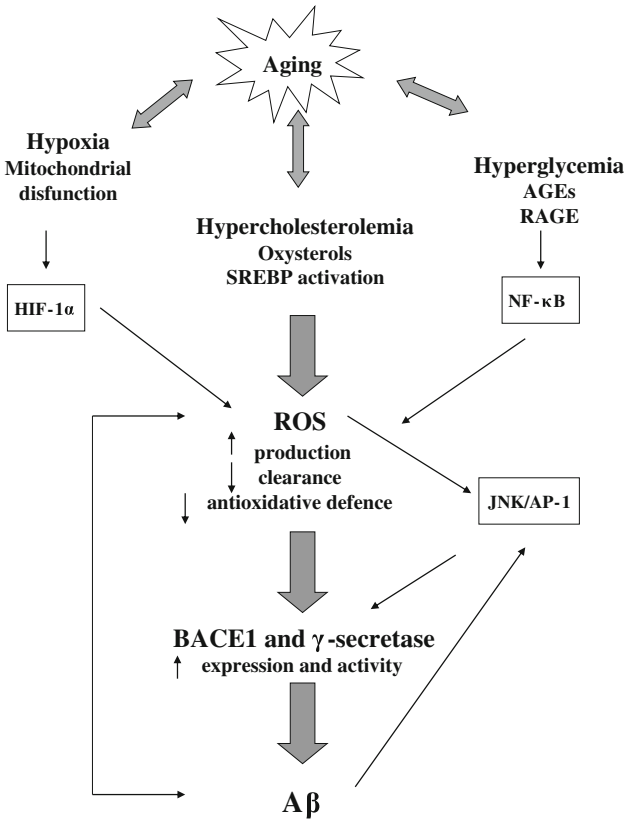

Fig. 1 Diagram sketching of the hypothesis that OS could be a basic common pathway of Aβ accumulation, as determined by different age-related risk factors

One of the most known and studied effects of Aβ is its ability to induce, and be induced by, OS. Several by-products of protein, lipid, and glucose oxidation seem to be elevated in the brain of patients with AD and to a lesser extent in the brains of healthy aged controls, as the burden of free radicals builds up proportionally to the duration of the disease (Borghi et al. 2007; Butterfield et al. 2001; Markesbery and Lovell 1998; Sayre et al. 1997). Both amyloid deposits and soluble Aβ seem to drive the accumulation of ROS (Behl 2005; Praticò 2008).

Transition metals, Cu(II), Zn(II), and mainly Fe(III) favor the neurotoxicity of Aβ, through their reduction, that yields hydrogen peroxide (H_2O_2) (Huang et al. 1999). It has been shown that Aβ residue Tyr-10 is a pivotal residue in driving the catalytic production of H_2O_2 in the presence of Cu(II). The phenoxy radical of this residue produced by the reaction with ROS causes neurotoxicity and acceleration in Aβ peptides aggregation (Barnham et al. 2004).

Another crucial residue of Aβ is Met-35, thus the substitution of Met with cysteine resulted in no protein oxidation in C. Elegans model (Yatin et al. 1999). An interesting downstream effect of Aβ-induced OS on lipids is the interference with membrane stability and the generation of calcium flow into the cells, leading to enhanced toxicity (Kirkitadze and Kowalska 2005). Moreover, lipid peroxidation induced by Aβ peptides impairs the function of ion-motive ATPase, glucose, and glutamate transporters and of GTP- binding protein, as the results of their covalent modification by aldehydic end products such as HNE.

Aβ is also able to induce oxidative modifications of proteins involved in cellular defence mechanisms against noxious stimuli as well as in energy pathways. In a murine experimental knock-in model of AD, harboring APP and PS1 mutations, a direct correlation between the excessive production of Aβ peptides and impairment of antioxidant enzymes, with consequent mitochondrial dysfunction, was reported (Anantharaman et al. 2006). These are further demonstrations of how increased OS induced by Aβ can lead to increased oxidative modifications of proteins and lipids leading to impaired cellular functions and cell death, and consequently cognitive impairment and AD pathology (Sultana et al. 2009).

Furthermore, Aβ can strike the production of pro-inflammatory mediators, such as TNF-α or IL-1β, leading to microglia activation, OS induction, and enhanced processing of APP to generate more Aβ (Akiyama et al. 2000; Atwood et al. 2003). In this connection, of particular interest is the report that APP promoter responds positively to inflammatory mediators; the inflammatory response leads to enhanced APP and Aβ productions and the involvement of OS is suggested by the finding that the iron chelation is able to reverse the phenomenon (Rogers et al. 2002).

OS may also be the cause of Aβ accumulation. Oxidant agents and oxidative products increase APP expression (Cheng and Trombetta 2004; Patil et al. 2006) and intracellular and secreted Aβ levels in many neuronal and non-neuronal cellular types (Frederikse et al. 1996; Misonou et al. 2000; Atwood et al. 2003; Murray et al. 2007).

We have extensively analyzed the transcriptional activation of BACE1, the key enzyme for Aβ production, first in response to OS, both in vivo and in vitro.

BACE1 gene promoter has a complex structure, carrying several transcription factor binding sites, such as for SP1, AP1, AP2, CREB, glucocorticoid receptor, NF-κB, and others (Sambamurti et al. 2004).

Different signaling pathways, such as SP1 (Christensen et al. 2004), JNK/AP1 (Tamagno et al. 2008), NF-κB (Buggia-Prevot et al. 2008), and p25/cdk5/STAT3 (Wen et al. 2008) have been suggested to control BACE1 transcription.

We and others have shown that the expression and activity of BACE1 is increased by oxidant agents (Tamagno et al. 2002; Tamagno et al. 2003; Tamagno et al. 2005; Kao et al. 2004; Tong et al. 2005). Several reports show that levels of BACE1 protein and activity are increased in brain of sporadic AD patients, compared to

normal age controls (Fukumoto et al. 2002; Holsinger et al. 2002; Yang et al. 2003; Zhao et al. 2007); moreover, there is a significant correlation of BACE1 activity and oxidative markers in sporadic AD tissues (Borghi et al. 2007).

We have proposed a sequence of events that link OS, BACE1 induction, and apoptotic cell death mediated by an overproduction of Aβ. First, we have shown that oxidant agents and HNE significantly increase the expression, protein levels, and activity of BACE1 in NT2 neurons (Tamagno et al. 2002; Tamagno et al. 2003). These events are followed by both an overproduction of Aβ peptides and morphological signs of apoptotic **c**ell death (Tamagno et al. 2005).

Then we have found that OS increases the γ-secretase activity in cultured cells and in vivo, and that the increased expression of BACE1 induced by OS is regulated by the γ-secretase activity (Tamagno et al. 2008). These results have important implications for the pathogenesis of sporadic AD. First, they suggest that OS, secondary to different AD risk factors, can increase the expression of both secretases, thereby enhancing Aβ production. Second, our data revealed the existence of a positive feedback loop in which γ-secretase activity results in up-regulation of BACE1 expression. Previously Minopoli et al. (2007) had shown a correlation between the induction of OS and the increase of γ-secretase cleavage on APP and then Jo et al. (2010) confirmed the finding that γ-secretase up-regulates BACE1 expression.

An increasing body of evidence implicates brain inflammation related to OS in the up-regulation of BACE1. Thus, the BACE 1 promoter has also a binding site for the transcriptional regulator proliferator-activated receptor γ (PPAR γ) (Sastre et al. 2006). Activation of PPARγ by non-steroidal anti-inflammatory drugs (NSAIDs) or PPARγ agonists cause repression of BACE1 gene promoter activity, while pro-inflammatory cytokines that reduces PPARγ levels lead to increased BACE1 mRNA (Sastre et al. 2006).

Several different mechanisms appear to be involved in the OS-mediated BACE1 up-regulation, and probably they overlap to promote the activation observed.

Our data strongly suggest that OS contributes to the pathogenesis of the common, sporadic, late-onset form of AD, and that, being able to up-regulate γ-secretase and BACE1, can be the molecular link between the two secretases.

These findings led us to think that either Aβ peptides or the APP intracellular domain (AICD) could be the APP derivatives from the γ-secretase cleavage responsible for BACE1 induction.

We investigated which derivative was responsible for BACE1 up-regulation. We first analyzed the effect of the AICD fragments 57 ad 59, the APP derivatives resulting from the γ-secretase cleavage of APP, as well as AICD 50 and 51 that are the ε cleavage derivatives (Passer et al. 2000; Tagami et al. 2008; Fukumori et al. 2006).

Transfection of different cell lines with the corresponding AICD constructs determined no change in BACE1 expression, thus our experiments ruled out the role of AICD in the over-expression of BACE1 and pointed to Aβ peptides (Giliberto et al. 2009). Thus, it is well known that mutant PS1 determines a drastic increase of Aβ42 species (Duff et al. 1996) and familial AD cases with PS1 mutations have mostly an increased ratio of Aβ42/40. We found that over-expression of PS1 mutants could alone determine an increase of BACE1 expression (Giliberto et al. 2009).

Instead, treating neuronal and neuroblastoma cells with 1 μM soluble Aβ42 increased BACE1 transcription, which was reverted if anti Aβ42 antibody was added to culture medium (Giliberto et al. 2009). Of note, Aβ40 has much less effect on BACE1 expression (Guglielmotto et al. 2011).

These findings reveal a novel function of Aβ peptides showing that Aβ42 is the player of a positive feedback loop from the γ-secretase cleavage on the BACE1 cleavage of APP (Fig. 2).

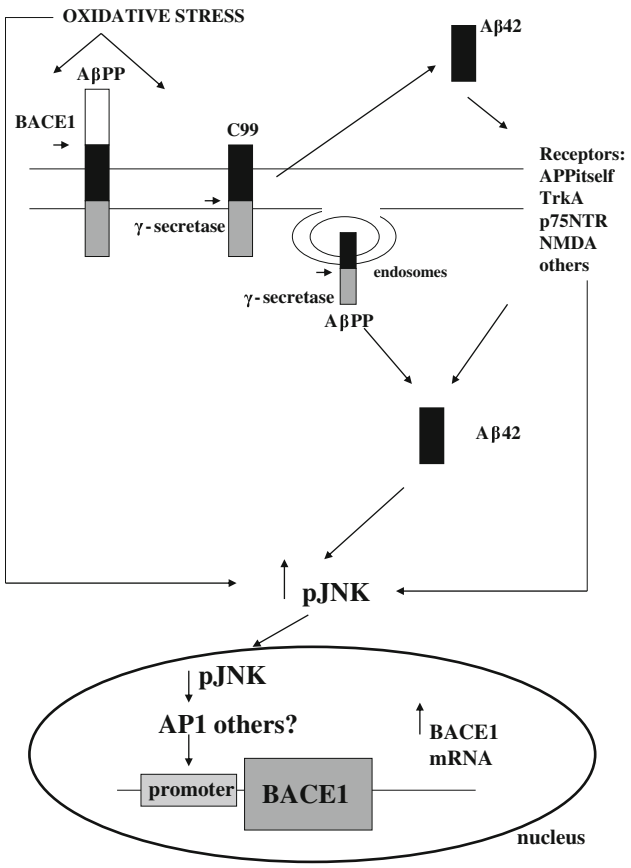

Fig. 2 Pathogenetic hypothesis in which OS fosters the expression and activity of BACE1 through the release of Aβ42 peptides and the activation of JNK/AP-1 pathway

It is not clear how Aβ42 could reach BACE1 transcription apparatus. There are many signaling pathways that seem to be regulated or at least affected by Aβ peptides. Among these Buggia-Prevot et al. (2008) found that Aβ42 was able to modulate BACE1 promoter transactivation and activity through an NF-κB-dependent pathway. Thus, an IkappaB kinase inhibitor prevents Aβ42-induced BACE1 promoter transactivation suggesting that NFkappaB could mediate this Aβ42-associated phenotype (Buggia-Prevot et al. 2008).

We recently found that also JNK/cjun pathway activation may be involved in the BACE1 up-regulation mediated by Aβ42 (Guglielmotto et al. 2011).

This pathway links all the pathological hallmarks of AD. JNK activation has been reported to regulate the phosphorylation of APP, leading to modulation of Aβ levels (Colombo et al. 2007; Colombo et al. 2009), as well as to mediate the phosphorylation of tau protein in vitro (Yoshida et al. 2004). Furthermore, the JNK pathway is shown activated in preclinical models of AD, including Tg2576 and Tg575/PS1^{P264L} transgenic mice (Flood et al. 2002; Puig et al. 2004), as well as in brains of AD patients (Zhu et al. 2003a; Zhu et al. 2003b; Lagalwar et al. 2006).

Indeed, we had previously found a significant activation of JNK/AP1 pathway by OS both in vivo and in vitro models, and the up-regulation of BACE1 was abolished when the pathway had been genetically or pharmacologically inhibited (Tamagno et al. 2008).

It remains to be determined how Aβ42 activates JNK pathway. Aβ is known to alter intracellular calcium hosmeostasis (Demuro et al. 2010), and JNK could be activated by the calcium/calmodulin dependent protein kinase II (CAMKII) (Wu et al. 2009) or by a PI3K inducing signal, mediated by calcium release (Assefa et al. 1999). Furthermore, it has been observed that Aβ-induced increase in intracellular calcium concentration stimulates BACE1 expression, resulting in accelerated Aβ generation, and that this process is mediated by the calcineurin-NFAT1 signaling pathway. NFAT1 is normally dephosphorylated by calcium-dependent manner by calcineurin, while it is phosphorylated and inactivated by JNK (Cho et al. 2008). Results of Ortega-Perez et al. (2005), however, demonstrated that, unlike other NFAT members, the transcriptional activity of NFATc2 appears up-regulated by JNK. Based on these notions, JNK-mediated phosphorylation of NFATs could play a differential physiological role among NFAT family members.

Cell surface receptors may be involved as well. Numerous proteins have been described to interact with Aβ directly or indirectly, such as AβPP itself, TrkA, p75NTR, some G proteins, NMDA, and AMPA receptors and many more. Thereby, the interaction of Aβ42 with multiple receptors is likely to produce the activation of the JNK/c-jun pathway. AβPP has been shown to function as a cell surface receptor that mediates neuronal cell death through the activation of JNK pathway (Hashimoto et al. 2003). Moreover, JNK pathway is shown involved in Aβ-driven signaling, as downstream of Aβ-RAGE interaction (Yan et al. 1996), TrKA/p75NTR (Yaar et al. 2007; Costantini et al. 2005), NMDA, and AMPA receptors (Di et al. 2010; Vieira et al. 2010). In general, the JNK signaling seems activated in AD (Lagalwar et al. 2006) and strongly correlates with the OS in AD models (Tamagno et al. 2005).

Also, besides being a means of scavenging Aβ from tissues and having a role in modulating APP endocytic trafficking, LRP family receptors and apolipoprotein E, of which the ε4 allele has a strong linkage with AD, could represent a way for Aβ to enter into neuronal cells (Bu et al. 2006; Jaeger and Pietrzik 2008) and interact with other still unidentified molecules to strike the signaling pathway that leads to BACE1 regulation.

Thus, the effects of Aβ on the cell are extremely complex. Being able to understand the specific signaling and to understand how soluble or insoluble Aβ induces its own production by up-regulating BACE1 expression would lead to new tools to interrupt the vicious circle, with potential therapeutics consequences.

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