Review article

Reactive astrocytes in Alzheimer's disease: A double-edged sword

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ABSTRACT

Alzheimer's disease (AD) is a chronic and fatal disease, in which neuronal damage at its late stage cannot be easily reversed. Because AD progression is caused by multiple factors including diverse cellular processes, studies on AD pathogenesis at the molecular and cellular level are challenging. Based on the lessons from unsuccessful neuron-focused research for an AD cure, non-cell autonomous mechanisms including brain inflammation and reactive astrocytes have recently been in the spotlight as potential therapeutic targets for AD. Studies have shown that reactive astrocytes are not only the result of inflammatory defense reactions, but also an active catabolic decomposer that acts by taking up amyloid beta toxins. Here, we give an overview of the characteristics of reactive astrocytes as pathological features of AD. Reactive astrocytes exert biphasic effects, that is, beneficial or detrimental depending on multiple factors. Many efforts have been put forth for defining and characterizing molecular signatures for the beneficial and detrimental reactive astrocytes. In the foreseeable future, manipulating and targeting each established molecular signature should have profound therapeutic implications for the treatment of AD.

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Contents

1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease that shows multimodal symptoms such as progressive cognitive impairment and changes in mood and behavior. AD comprises various stages of severity, such as pre-clinical AD, mild cognitive impairment (MCI), and AD dementia (Masters et al., 2015). The majority of AD cases (over 95%) appear in sporadic form, related to environmental factors or aging, whereas familial AD (less than 5% of cases) is caused by inherited mutations of AD-related genes such as amyloid precursor protein (APP) (Goate et al., 1991), presenilin 1 (PS1), or presenilin 2 (PS2) (Levy-Lahad et al., 1995; Sherrington et al., 1995). These genes are all related to the increase of amyloid beta production, which is one of the major features of

AD. Because it is believed that the accumulation of amyloid beta aggregates triggers hyperphosphorylation of tau and causes neurodegeneration in AD, therapeutic strategies for AD are based on the "amyloid hypothesis," and the AD research field has undoubtedly put enormous efforts into regulating the level of amyloid beta over the last few decades. Nevertheless, the results remain largely ineffective. Anticipated phase III clinical trials of amyloid beta antibody (Solanezumab, funded by Eli Lily) and BACE inhibitor (Verubecestat, funded by Merck) were recently declared to have failed (Doody et al., 2014; Hawkes, 2017). Meanwhile, currently approved drugs for AD neurodegeneration targets have a very limited time window regarding their effect of slowing the disease progression, and these drugs are therefore not an effective treatment for the disease. These serial failures challenge the current amyloid hypothesis and the neurocentric view that many pharmaceutical companies have spent billions of dollars on, and necessitate a paradigm shift in the still obscure etiology of AD.

Neuronal death is a late-phase event in AD and represents a therapeutically irreversible state. However, reversibility is the key to find new strategies for an ultimate AD cure. Therefore, researchers have recently focused on the brain inflammation occurring before neurodegeneration in AD pathogenesis, and it is believed that targeting inflammatory mechanisms can reverse the process of disease progression. In this review, we will present an overview of the main characteristics of AD and the role of brain inflammation, especially the role of reactive astrocytes, on AD pathogenesis.

2. Features of AD

Patients with AD show toxic protein aggregates such as amyloid beta and tau tangles (Taylor et al., 2002). In 1906, Alois Alzheimer first observed amyloid plaque and neurofibrillary tangles (NFTs), which are histopathological hallmarks of AD, in the brains of patients with AD. Amyloid beta is normally produced and degraded in healthy individuals (Haass et al., 1993; Mawuenyega et al., 2010), although its role is not fully understood. It occurs in the form of monomers, oligomers, protofibrils, fibrils, and amyloid beta plaques. Among amyloid peptides of various lengths, the peptide of a length of 40–42 amino acids has aggregating properties, and the fibrillary form of amyloid beta is the principal component of amyloid plaques shown in extracellular space. When amyloid beta is progressively accumulated and levels are aberrantly elevated, the incidence rate of AD is significantly increased. It is in fact known that the amyloid beta clearance mechanism is disrupted in patients with AD (Mawuenyega et al., 2010), which means that maintaining appropriate levels of amyloid beta is important in physiological conditions. It has been reported that amyloid beta deposition starts decades before cognitive decline, and brain atrophy is detected by amyloid beta PET (position emission tomography) imaging (Villemagne et al., 2013). The Pittsburgh compound B (PiB), a radioactive carbon-11 analogue of the fluorescent amyloid due thioflavin-T62, binds to fibrillary amyloid beta and thus makes amyloid beta imaging possible *in vivo* (Cohen et al., 2012; Mathis et al., 2003). In contrast, NFTs accumulate in intraneuronal regions and are formed through hyper-phosphorylation of tau proteins. Tau tangles are correlated with disease severity (Augustinack et al., 2002; Bierer et al., 1995). Moreover, it is known that tau pathology itself can cause neurodegeneration(Ballatore et al., 2007).

Brain inflammation is ubiquitously observed in the AD brain, and mainly consists of glial activation, such as astrogliosis, and microglial activation (Serrano-Pozo et al., 2013; Itagaki et al., 1989). In his original descriptions, Alois Alzheimer firstly mentioned glial changes having fibers and large deposits in brain of patient with AD (Fig. 1C). He observed the morphological alterations of glial cells in the brain of his second patient, Johann F. Credit and drew the hyper-

trophied glial cells surrounding the plaque. (Fig. 1B). However, the precise role of those morphologically altered glial cells, which now we refer to reactive astrocytes, is largely unknown. In amyloid beta-overexpressing mice, an animal model of AD, reactive astrocytes and activated microglia appear surrounding amyloid plaques. As the number of plaques increases, gliosis becomes severe (Jo et al., 2014). It is known that the severity of gliosis is correlated with disease severity (Simpson et al., 2010). Despite its pervasive existence in the AD brain, gliosis has long been considered an epiphenomenon following neurodegeneration. However, since temporal correlation studies showed that inflammatory changes precede the clinical symptoms of AD and amyloid beta deposition (Tarkowski et al., 2003), research has increasingly been focused on the importance of immune states in AD pathogenesis. However, the contribution of glial cells such as astrocytes and microglia on AD pathogenesis is largely unknown.

Neurodegeneration is a final cellular symptom of AD. Neuronal death takes place in brains of patients with AD. The proposed mechanisms of neurodegeneration include excitotoxicity via glutamate, nitrosative stress, tauopathy, and axonal degeneration leading to programmed cell death (PCD) (Cusack et al., 2013) and/or autophagic cell death (ACD) (Nixon, 2013). When the extracellular glutamate concentration is increased above physiological levels, NMDA-mediated excitotoxicity leads to the death of neurons (Hynd et al., 2004; Coyle et al., 1981). Nitrosative stress is caused by excess production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which lead to cell death by nitration of proteins (Nakamura and Lipton, 2007; Lipton et al., 1993). Tauopathy consists of neurofibrillary tangles that are made from hyperphosphorylated tau protein aggregation and directly kill the cell (Spillantini and Goedert, 2013; Yoshiyama et al., 2007). Tau hyperphosphorylation is mediated by the GSK3 beta pathway, which is activated by oxidative stress (Zhang et al., 2005). However, the etiology of neurodegeneration is not clear. In AD, brain atrophy is also shown on MR images of human patients (Zhang et al., 2011). The degree of brain atrophy correlates with the neurofibrillary tangle pathology defined by Braak stage, while it is not correlated with the amyloid beta deposition (Braak and Braak, 1991; Whitwell et al., 2008; Josephs et al., 2008).

To attenuate the disease progression, several drugs are being used such as acetylcholinesterase inhibitors (Rivastigmine, Galantamine, Donepezil) and N-methyl D-aspartate receptor antagonist (Memantine). Rivastigmine, Galantamine, and Donepezil are administered to patients with mild to moderate AD (Cruz Jentoft and Hernandez, 2014; Hirsch, 2006; Greenberg, 2000), whereas Memantine is prescribed to patients with moderate to severe AD (Finucane, 2004). However, these drugs cannot reverse the disease progression and have many adverse side effects (Liu et al., 2002; Inglis, 2002). These shortfalls of the currently available AD drugs probably come from the fact that we still do not have a complete and detailed picture of the sequence of events during the progression of AD. There is thus an urgent need for finding therapeutic targets according to the time-ordered sequence of events during disease progression and for developing new drugs for AD.
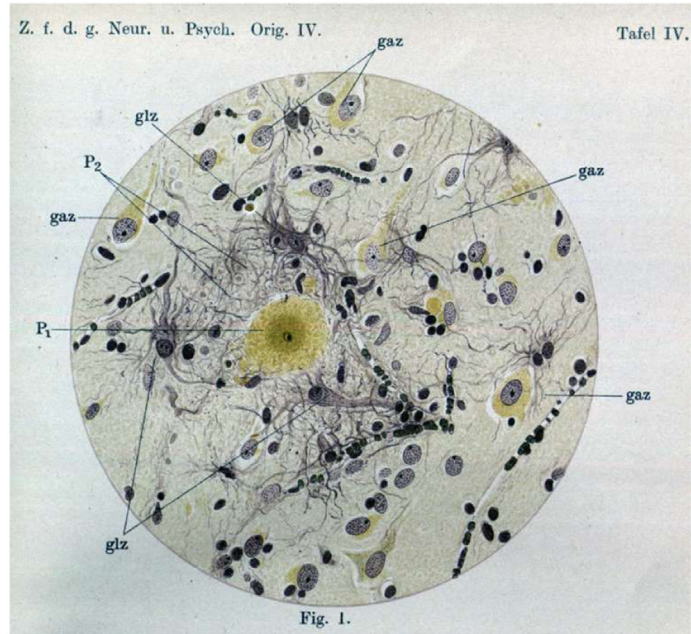
3. Brain inflammation in AD pathogenesis

It is generally considered that identification of the time-ordered sequence of pathogenic events is crucial for elucidating the causal relationship between known biomarkers and AD (Jack et al., 2010). The temporal order of AD biomarkers in disease progression needs thus to be addressed. Research shows that inflammatory signals in the brain, including glial activation, are detected early during the pre-symptomic phase of AD progression with amyloid beta production (Jack et al., 2010). Recently, NSAIDs (non-steroidal

A

B

C-1

Die Glia hat reichlich Fasern gebildet, daneben zeigen viele Gliazellen große Fettsäcke.

C-2 The glia had abundant formed fibers; in addition, many glia cells showed large deposits.

Fig. 1. Observation of glial changes in brains of patients with AD by Alois Alzheimer. **A.** Alois Alzheimer (German, 1864–1915). **B.** Drawing of hypertrophied glia and plaques from a histological section of Alzheimer's second patient, Johann F. Credit, 1911. **C.** (1) Primary report of glial changes in patients with AD in 1906. (2) English translation of C-1.

anti-inflammatory drugs) have been shown to be effective for AD symptoms (Lichtenstein et al., 2010; Szekely and Zandi, 2010). In addition, an animal study showed, surprisingly, that systemic immune challenges caused by the viral mimic polyriboinosinic-polyribocytidilic acid sufficiently induced AD pathology such that tauopathy and amyloid plaques are formed (Krstic et al., 2012), proposing that brain inflammation can be an initial factor for AD pathogenesis. Related to this phenomenon, inflammation in the brain is considered to be an important factor for AD progression. Gliosis shown in AD is composed of activated microglia as well as reactive astrocytes. Microglia also become activated in an injured condition and show morphological changes from a ramified into an amoeboid shape. Amoeboid-like microglia surround amyloid plaques and undergo phagocytosis by engulfing amyloid beta peptide (Fu et al., 2014). When microglia are activated, proinflammatory molecules such as ROS and cytokines are released, leading to neurotoxicity (Cunningham, 2013). Astrocytic reactivity is correlated with the severity of AD. However, the contribution of reactive astrocytes to the pathogenesis of AD is still elusive.

4. Reactive astrocytes in AD

4.1. General description/features of reactive astrocytes

Reactive astrocytes are an activated form of astrocytes in response to toxic materials. Astrocytes change their properties morphologically, transcriptionally, and functionally. Regarding morphological changes in response to toxic materials, astrocytes show hypertrophy and process ramification. Reactive astrocytes increase their cell body size and the thickness of astrocytic processes. In addition, the branching of astrocyte processes becomes complex and is reorganized with increasing reactivity (Wilhelmsson et al., 2006), as has been shown in an increased number of astrocyte processes and a polarization toward the injury site (Bardehle et al., 2013) or toxic aggregate. Glial fibrillary acidic protein (GFAP) has long been considered a standard marker of reactive astrocytes (Sofroniew, 2009). In addition to GFAP, other intermediate filament proteins such as vimentin and nestin are also upregulated in reactive astrocytes. Astrocyte reactivity has been demonstrated as morphological hypertrophy, since gliosis was firstly reported through immunostaining using GFAP antibodies in the brains of patients with AD (Bignami et al., 1972).

Reactive astrocytes show a broad and graded spectrum of reactivity, and are heterogeneous in morphology, gene expression, and function (Anderson et al., 2014). Severe injury (Simon et al., 2011) or stroke (Shimada et al., 2011) cause proliferation of astrocytes as well as severe reactiveness (Sofroniew, 2009), whereas mildly reactive astrocytes do not proliferate at distant regions from the injury site. The proliferation of reactive astrocytes is correlated with the disruption of individual domains of astrocytes. Originally, astrocytes have their unique domains that do not overlap with each other in the normal brain (Bushong et al., 2002). However, this individual domain is disrupted in the region where severely reactive astrocytes are formed (Wanner et al., 2013). According to

the experimental setup, there are differences in the state of pro-liferation and domain disruption. Astrocyte proliferation is rarely shown in current experimental models of AD (0–3%) (Sirko et al., 2013) and reactive astrocytes in the Tg2576 AD mouse model do not lose their domain organization (Oberheim et al., 2008), whereas in experimental models of epileptic seizure, individual domains of each astrocytes are not preserved (Oberheim et al., 2008). Additionally, lipopolysaccharide (LPS)-induced models of reactive astrocytes show no increase in the number of astrocytes *in vivo* or *in vitro* (Zamanian et al., 2012; Liddelow et al., 2017).

To understand the role of reactive astrocytes, there have been many attempts to investigate transcriptional regulation in purified astrocytes of various injury or disease models. In LPS and MCAO (Middle Cerebral Artery Occlusion) mouse models, which accom-pany the induction of reactive astrocytes, multiple genes are shown to be upregulated in acutely purified astrocytes (Zamanian et al., 2012). In the subsequent study, these altered genes are shown to be heterogenous between the two conditions (Liddelow et al., 2017). The authors characterized the altered gene expression and sug-gested that A2-reactive astrocytes in the MCAO model can have beneficial or protective functions, whereas A1-reactive astrocytes in the LPS-induced brain have neurotoxic properties. Moreover, the authors tried to relate the phenotype of A1-reactive astrocytes to many neurodegenerative diseases including AD (Liddelow et al., 2017). Because it is considered that the biphasic effects of reac-tive astrocytes depend on the reactivity of astrocytes (Sofroniew, 2009), A1- and A2- type might have different reactivity in each experimental setup, LPS or MCAO. However, there are no suitable experimental models that can manipulate the reactivity of astro-cytes in order to test and generalize this idea.

To mimic reactive astrocytes, various injury models have been used to induce reactive astrocytes, such as stab wound injury, LPS and MCAO models. These not only induce reactive astrocytes but also induce microglial activation or neuronal injury directly. In con-trast, knockout mice of GFAP and vimentin genes or transgenic mice carrying GFAP-TK(Thymidine kinase under GFAP promoter) have been used to abolish the morphological changes of reactive astrocytes or to ablate proliferating reactive astrocytes, *in vivo*, respectively (Kamphuis et al., 2015; Myer et al., 2006; Faulkner et al., 2004). However, these systems both have serious limitations, with the former limiting the effects of morphological arborization of reactive astrocytes and the latter rendering the environment inflammatory by ablating brain cells. These systems cannot dis-tinguish between the cause and the effects of phenomena related to reactive astrocytes. Therefore, to solve these limitations, devel-oping suitable experimental models to exclusively induce and manipulate the reactivity of astrocytes *in vivo* are undoubtedly needed. Moreover, understanding the mechanism underlying the induction of reactive astrocytes is important to study the function of reactive astrocytes.

4.2. Altered characterization of reactive astrocytes related to AD

In the brain of patients with AD, reactive astrocytes are detected on PET imaging, with the PET tracer ^{11}C-deuterium-L-deprenyl (^{11}C-DED) used to measure monoamine oxidase B located in astro-cytes (Carter et al., 2012). In AD animal models, reactive astrocytes are also detected before amyloid plaque formation (Heneka et al., 2005). It is known that reactive astrocytes respond to amyloid beta, morphologically, metabolically, and functionally (Pike et al., 1994; Allaman et al., 2010; Yan et al., 2013; Carbonaro et al., 2009; Sollvander et al., 2016). Amyloid beta plaques are associated with reactive astrocytes, and amyloid beta induces an GFAP increase in astrocyte culture(Pike et al., 1994). Reactive astrocytes are also shown in human patients with AD (Owen et al., 2009; Carter et al.,

2012). At the same time, reactive astrocytes produce amyloid beta (Zhao et al., 2011).

4.2.1. Metabolic plasticity

In injury or toxic conditions, astrocytes become reactive and undergo changes in their metabolic profile, and they adapt and optimize their metabolism to produce energy in injured conditions. Astrocytes have been shown to take up amyloid beta and degrade it to clear plaques (Wyss-Coray et al., 2003). It has also been reported that amyloid beta-treated astrocytes change their metabolic pro-file and improve their glucose utilization (Allaman et al., 2010). Amyloid beta production and clearance mechanisms have been shown to be crucial for the pathogenesis of AD (Mawuenyega et al., 2010; Kizilarslanoglu and Ulger, 2015). Moreover, patients with AD showed a decrease in the kinetics of amyloid beta clear-ance (Mawuenyega et al., 2010). Degradative mechanisms such as autophagy and ubiquitination have been suggested to be involved in the response to amyloid plaques (Takalo et al., 2013). It is known that defective autophagy mechanisms cause neurodegeneration (Kizilarslanoglu and Ulger, 2015), but how autophagy mechanisms are involved in astrocyte functions in AD conditions is not known. It was demonstrated that reactive astrocytes near amyloid plaques produce more putrescine, a type of polyamine degraded from toxic molecules, and degrade putrescine into GABA via monoamine oxi-dase B (MAO-B) (Jo et al., 2014). The abundance of putrescine and autophagy system could be somehow linked but this possibility needs to be tested in the future.

Monoamine oxidase B (MAO-B), which is primarily expressed in astrocytes and localized in the outer membrane of mitochon-dria, catalyzes the oxidative metabolism of monoamines such as benzylamine, acetylputrescine, or dopamine. Decades ago, it was first reported that MAO-B is expressed in astrocytes (Levitt et al., 1982) and that its activity is increased in reactive astrocytes, by means of ^{3}H-L-deprenyl emulsion autoradiography (Ekblom et al., 1993). Related to MAO-B, the detection of reactive astrocytes by PET imaging was performed using MAO-B probes. In patients with MCI, 11C-DED, labeled deprenyl, which is an MAO-B inhibitor, was increasingly detected, compared with control subjects(Carter et al., 2012). Moreover, the increased 11C-DED levels were correlated with the decrease of grey matter density measured by MRI in 11C-PIB-positive MCI patients and the signal increase of amyloid beta fibrils measured by 11C-PIB-PET (Choo et al., 2014; Carter et al., 2012). Taken together, MAO-B activity, which can represent the reactivity of astrocytes, has strong correlation with AD pathogene-sis.

4.2.2. Gliotransmitters

Gliotransmitter released from astrocytes are increasingly found, and include glutamate, GABA (gamma-aminobutyric acid), ATP (adenosine triphosphate), and D-serine. When astrocytes become reactive, the releasing level of gliotransmitters is changed, which affects neuronal activity. Recently, it has been reported that GABA contents are increased in reactive astrocytes surrounding amy-loid plaques (Fig. 2A). GABA is synthesized from putrescine, a type of polyamine, by activation of monoamine oxidase B (MAO-B) (Fig. 2B). When levels increase, more GABA is released into the extracellular space, which inhibits neuronal activity and impairs memory abilities in AD mouse models (Jo et al., 2014). Increased tonic inhibition in the dentate gyrus region of the 5XFAD mouse brain has also been shown (Wu et al., 2014). The authors sug-gested that GABA uptake by GABA transporters and extracellular GABA concentrations are effective in affecting synaptic plasticity and memory abilities. The role of GABA in terms of protective versus detrimental action is unclear. However, one can specu-late that the role of GABA is perhaps for protection of neurons from over-excitation at the expense of memory impairment. In
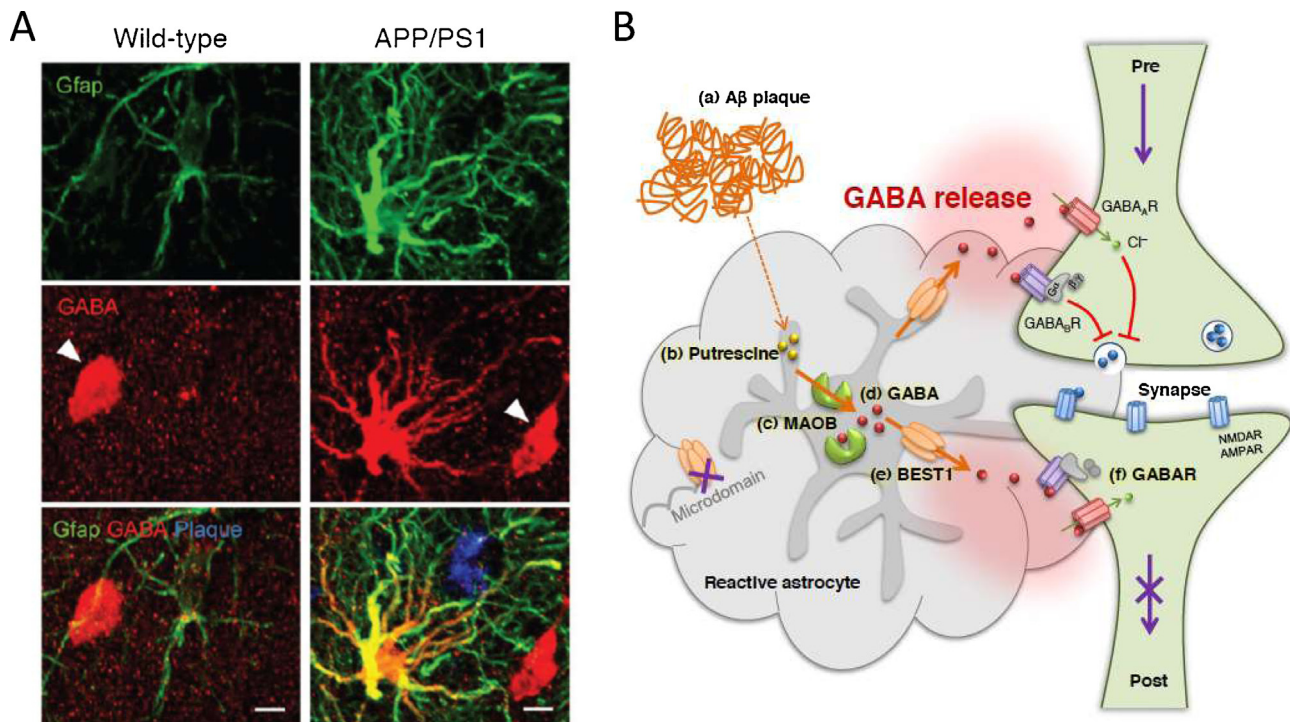
Fig. 2. A. Immunostaining of GABA and GFAP in the molecular layer of DG from wild type and APP/PS1, AD model mouse. **B.** Model diagram of GABA release from reactive astrocytes in animal model of AD.

contrast, glutamate is released from astrocytes in response to amyloid beta. The released glutamate activates extrasynaptic NMDA receptors and mediates amyloid beta-induced synaptic depression and spine loss (Talantova et al., 2013). Glutamate release by TNF (tumor necrosis factor) alpha application is impaired in PDAPP mice, a type of AD model mice (Rossi et al., 2005). Purines, another kind of gliotransmitter comprising ATP and adenosine, is also released from astrocytes. Amyloid beta application on cultured astrocytes releases ATP (Jung et al., 2012) through Cx43 (connexin 43) hemichannels (Orellana et al., 2011). Recent reports also showed that ATP is increasingly released via hemichannels from reactive astrocytes around amyloid plaques in APP/PS1 mice. The released ATP acts on astrocytic P2Y1 receptors and increases Ca^{2+} concentrations in an autocrine manner (Delekate et al., 2014).

4.2.3. Oxidative and nitrosative stress

Reactive oxygen species (ROS) are generated during normal cellular metabolism and play multiple roles in CNS functions, as for example maintaining cognitive function, neurotransmitter secretion, brain homeostasis, and neuroprotection. ROS contain hydrogen peroxide (H_2O_2), superoxide (O_2^-), and hydroxyl radical (OH^-). Generally, ROS levels exceeding physiological ranges have biphasic effects on cell viability. Low concentrations of ROS stimulate cell proliferation, whereas high concentrations have harmful effects on enzymes, membrane lipids, and DNA, which consequently leads to cell death (Liou and Storz, 2010). The homeostasis of ROS levels in the brain is crucial for maintaining brain functions, and for that reason, the brain is equipped with various ROS-producing or −eliminating enzymes, such as peroxidase, oxidase, superoxide dismutase (SOD), and NADPH oxidase (NOX).

The ROS-mediated pathway is related to AD. In patients with AD, it has been suggested that ROS levels are increased and oxidative stress occurs(Markesbery, 1999). For this reason, targeting ROS or ROS-related enzymes has been a therapeutic strategy in AD. Antioxidants such as vitamin E, flavonoids such as rutin, and

carotenoids have shown neuroprotective effects in animal models and are expected to alleviate the disease progression (Gutierrez-Merino et al., 2011; Behl, 1999). A phase III trial combining vitamin E with memantine and vitamin E with selenium was recently conducted. However, the additive effect of vitamin E and memantine was not observed, while only vitamin E treatment was effective in cognitive decline of mild to moderate AD (Dysken et al., 2014). Moreover, combining vitamin E with selenium was not effective in prevention of AD (Kryscio et al., 2017; Dysken et al., 2014). These disappointing effects of antioxidants in clinical test could be due to improper dosage, time of interventions, or combination of antioxidants. It is known that the abnormal concentration of antioxidants can act as a pro-oxidant (Herbert, 1996), which can be one of factors for failure of antioxidant in AD drug development. Moreover, improper selection of subjects for clinical tests could be another reason: because it is known that oxidative stress occurs at relatively early time in AD progression and slowly develops to the point of no return, the treatment of antioxidants at late stage of AD would possibly results in clinical failure. Finally, the lack of proper combination of the existing antioxidants could be a potential reason for the therapeutic failures, considering their synergetic effects with each other. (Persson et al., 2014)

Astrocytes are important for neuroprotection by generating antioxidants such as glutathione. Astrocytes play crucial roles in defensive action by producing antioxidant molecules against oxidative stress, and have protective effects on neurons, which are vulnerable to hydrogen peroxide toxicity (Desagher et al., 1996). In contrast, astrocytes produce hydrogen peroxide in response to amyloid beta treatment (Allaman et al., 2010). In reactive astrocytes, ROS levels are increased and ROS-producing enzymes are upregulated. Cultured astrocytes release more ROS in response to amyloid beta through the pentose-phosphate pathway, and become toxic to co-cultured neurons (Allaman et al., 2010). The biphasic effects of astrocytes can be dependent on the level of ROS production, which is correlated with the amount of amyloid beta
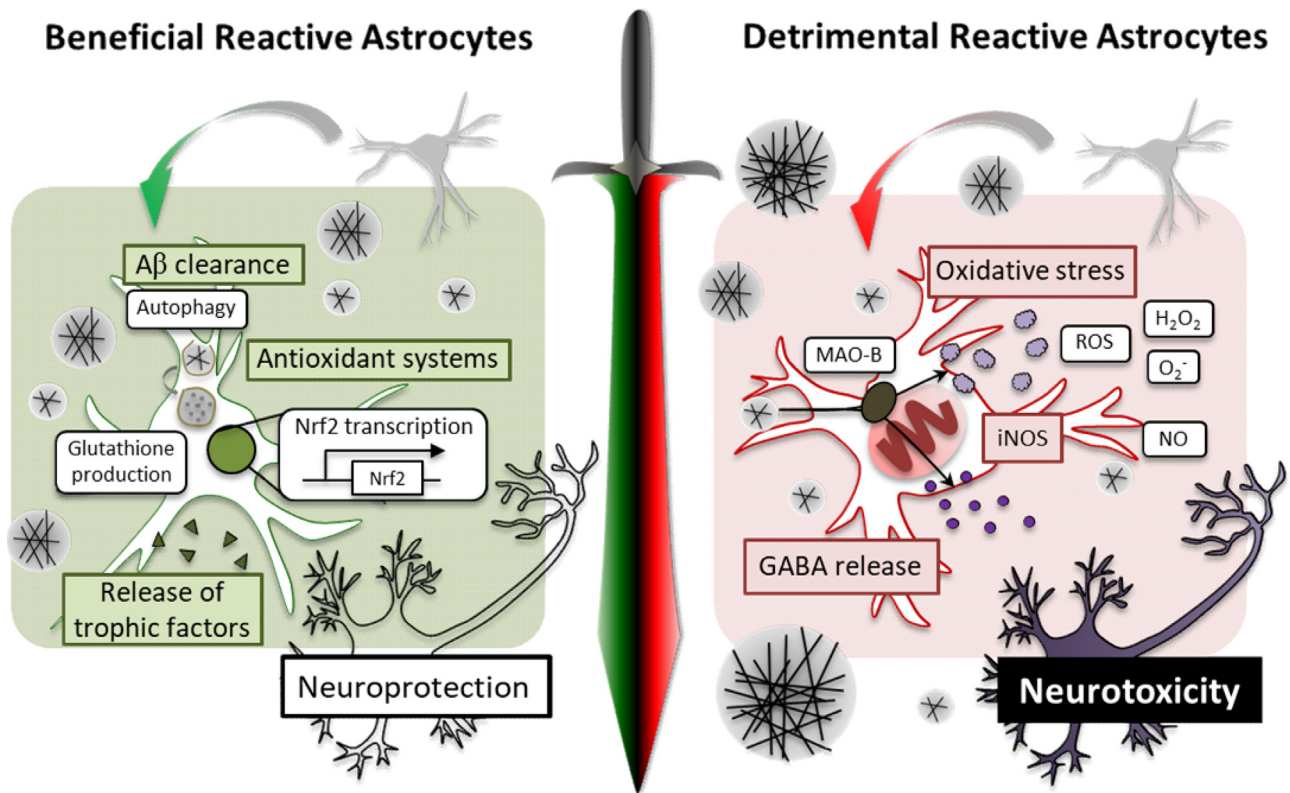
Fig. 3. Beneficial and detrimental reactive astrocytes in AD; a double-edged sword.

toxin (Narayan et al., 2014). The more amyloid beta toxins, the more oxidative degradation, producing a large amount of ROS. Because ROS itself can trigger various signaling pathways to induce antioxidant systems or trophic factor expression, the low level of ROS may exert beneficial functions for neuroprotection (Wang et al., 2006). On the other hand, the exaggerated ROS can turn on iNOS expression, which induces nitrosative stress and toxic nitration in neurons (Bagheri et al., 2017; Akama and Van Eldik, 2000). These suggests that the level of ROS in astrocytes can act as a key determinant in the fate of reactive astrocytes affecting neuronal functions. Therefore, reactive astrocytes act as a double-edged sword having both beneficial and detrimental functions in neuronal viability against toxic environment, according to the level of ROS production (Fig. 3).

ROS activates signaling pathways such as the NFκB pathway and induce morphological changes through GFAP expression in astrocytes (Akama and Van Eldik, 2000; Carrero et al., 2012). The small Rho GTPase, Ras, is known to be involved in the GFAP increase(Kalman et al., 1999). This raises a possibility that the hypertrophy of astrocytes, which has been generally used to represent the reactivity by itself, is the consequence of ROS accumulation. It would be very interesting to investigate this possibility in future studies

Reactive nitrogen species (RNS) contain nitric oxide (NO), which is produced by nitric oxide synthase (NOS). Nitric oxide itself is not particularly toxic *in vivo*, but it can react with superoxide to form the powerful oxidant peroxynitrite. NOS is required for the synthesis of NO, and there are three isoforms of NOS, namely iNOS, eNOS, and nNOS. Out of these three isoforms, iNOS is expressed in glial cells as response to pro-inflammatory cytokines and amyloid beta toxins (Akama and Van Eldik, 2000; Sheng et al., 2011). In the AD brain, iNOS is overexpressed in reactive astrocytes(Luth et al., 2001). Another study showed that in AD, there is activation of microglia, which in turn activates iNOS, that results in excess NO

release by microglial cells and consequently in immunomodulation and neuronal damage(Cherry et al., 2014).

Oxidative stress and nitrosative stress have been considered as significant contributors to AD progression. However, despite a long history of research in various fields, significant progress regarding AD treatment has not been demonstrated. The reasons can include the elusive cellular sources of each ROS or ROS-generating/degrading enzymes and the inefficient antioxidants to scavenge ROS. In this regard, research on the molecular and cellular mechanisms of ROS-related pathway in AD pathogenesis would contribute to understanding the role of oxidative stress in AD. Moreover, development of potent antioxidants would take a leap forward to AD therapeutics.

5. Therapeutic implications

The therapeutic strategies for multifactorial AD should be designed for each pathogenic time course. Reactive astrocytes, as an early sign of AD, have therapeutic implications in various diverse aspects. They represent a double-edged sword, with both good and bad effects on brain functions, possibly depending on their level of reactivity (Fig. 2). Taking up and eliminating toxic materials such as amyloid beta can be considered as positive functions of astrocytes, as these processes could directly prevent neuronal injury by toxins. Thus, drugs promoting amyloid beta-clearing mechanisms such as autophagy or ubiquitin systems have therapeutic potential for AD. Additionally, releasing trophic factors and activating antioxidant systems such as Nrf2(Nuclear factor (erythroid-derived 2)-like 2) transcription in reactive astrocytes are beneficial for brain functions. Therefore, facilitating these processes could be helpful for the treatment of AD. In contrast, the buffering effects by astrocytes through active clearance of amyloid beta toxins can lead to changes in their metabolic status and

paradoxically over-produce toxic metabolites, inhibitory transmitters, and/or ROS. The accumulation of these factors chronically transforms astrocytic properties and changes their functions to neurotoxic and harmful. Therefore, drugs aimed at metabolites- or ROS-generating systems have therapeutic potential. The regulation of ROS-producing enzymes or the activation of antioxidant systems could maintain an appropriate oxidative status and block harmful effects on nearby neurons. Furthermore, controlling astrocytic GABA levels by manipulating MAO-B activity could restore the memory impairments found in AD. To develop astrocyte-specific drugs, investigating the astrocyte-specific mechanisms underlying amyloid beta toxin clearance and metabolite production are crucial for finding future therapeutic targets.

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