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## Metabolic Dysfunction of Astrocyte: An Initiating Factor in Beta-amyloid Pathology?

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### Abstract

Astrocytes, the most important energy regulator in the brain, support brain energy needs. In the meantime, numerous studies have demonstrated that impaired brain glucose metabolism is closely linked to abnormal astrocytic metabolism in AD. Indeed, the interaction between amyloid plaques and perturbed astrocytic homeostasis contributes to AD pathogenesis and astrocytic metabolic dysfunction is thought to be a trigger for A $\beta$  pathology through oxidative stress and neuroinflammation. Moreover, astrocytic metabolic dysfunction may regulate A $\beta$  generation via modulating proteolytic processing of amyloid precursor protein (APP) by  $\beta$ -secretase,  $\gamma$ -secretase, and  $\alpha$ -secretase, and may also modulate APP post-translational modifications such as glycosylation, phosphorylation, and tyrosine sulfation. While it is known that metabolic dysfunction of astrocytes contributes to the failure of A $\beta$  clearance, it has also been reported that such dysfunction has neuroprotective property and exhibits no detrimental outcomes. Therefore, the exact role of astrocytic metabolic dysfunction in A $\beta$  pathology remains to be further investigated.

### Keywords

Alzheimer's disease; astrocytes; beta-amyloid protein; metabolic dysfunction

### 1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder leading to cognition decline, behavioral symptoms, and eventual loss of social or occupational function. Beta-amyloid (A $\beta$ ) plaques (extracellular A $\beta$  deposition) and neurofibrillary tangles (NFT, intracellular deposits of hyper-phosphorylated tau protein) have been identified as two classical pathological hallmarks of AD [1-3]. Accordingly, numerous studies have focused on A $\beta$  generation and deposition as well as on NFT formation as the triggering factors for AD occurrence [4, 5].

By maintaining brain homeostasis, astrocytes are the most important energy regulator in the brain [6, 7]. Indeed, astrocytes play a role of metabolic activation in the brain and support

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brain energy needs [7, 8]. Over the past decade, numerous studies on astrocytes attempting to elucidate AD etiology have evidenced that impaired brain glucose metabolism is closely associated with abnormal astrocytic function in AD [9-11]. Firstly, the interaction between amyloid plaques and perturbed astrocytic homeostasis has been found in AD. Secondly, it is via oxidative stress and neuroinflammation that metabolic dysfunction of astrocyte contributes to  $A\beta$  pathology [12]. In addition, it is known that metabolic dysfunction of astrocyte regulates proteolytic processing of APP by  $\beta$ -secretase,  $\gamma$ -secretase, and  $\alpha$ -secretase [13]. Moreover, metabolic dysfunction of astrocytes may also be a regulator of APP post-translational modifications such as glycosylation [14], phosphorylation, and tyrosine sulfation [15-18], and may lead to failure in  $A\beta$  clearance [19, 20].

This review focuses on the role of metabolic dysfunction of astrocytes in  $A\beta$  pathology. An overview is provided for the proposed general pathogenic mechanisms of metabolic dysfunction of astrocyte in  $A\beta$  pathology that are mainly via oxidative stress and neuroinflammation, regulation of proteolytic processing of APP and APP post-translational modification, and failure in  $A\beta$  clearance. Finally, the possibility of improving astrocytic function as a potential target for AD prevention and treatment is also discussed.

## 2. Astrocytes

Astrocytes, large and star-shaped neuroglial cells with many branches, are specialized glial cells that out-number neurons by more than five-fold [21]. They play multifunctional roles including physical support, nutritional supply, and biochemical support to the blood-brain barrier (BBB) and neurons [22-24] as well as to the repair and scarring of injury [25, 26]. Astrocytes are critical mediators of brain homeostasis, such as maintaining the balance of ions and the integrity of BBB in the central nervous system, communicating with neurons and other important structures, releasing growth factors, and regulating neurotransmitter levels [24, 27, 28]. Numerous studies have indicated that astrocytes are involved in all types of brain pathologies from acute lesions such as trauma or stroke to chronic neurodegenerative processes such as AD, Parkinson's disease, multiple sclerosis [29-33], and psychiatric diseases. Many studies also reported a role of astrocytic degeneration and atrophy in various neurodegenerative disorders [34-36].

## 3. Abnormal glucose metabolic dysfunction in astrocytes: a direct link to AD

Glucose, an essential energy source for the brain, is oxidized through sequential metabolic pathways including glycolysis, the tricarboxylic cycle, and oxidative phosphorylation. Glucose can also be stored as polysaccharide glycogen in the brain. Medical scientists confirm that low glucose metabolism is the early warning signs of AD [37, 38], and glucose metabolic failure is an early event in neurodegenerative disease represented by altered expression of nutrient transporters, metabolic enzymes and molecular components of cellular respiration [39, 40]. Therefore, it is well established that brain glucose metabolism is impaired in AD [41, 42] and alterations in cerebral blood flow and oxygen consumption would decrease most severely with age and neurodegenerative process accompanied by low glucose metabolism [43, 44]. It has been reported that in AD glucose hypometabolism, mostly due to glycolytic breakdown and pyruvate oxidation [45, 46], promotes  $A\beta$  pathology, facilitates abnormal hyperphosphorylation of tau [47], damages synaptic transmission function, and leads to the occurrence of cognitive impairment [48, 49].

Astrocytes are thought to play a role in metabolic activation in the brain by promoting glycolysis, glycogenolysis activities, and production of lactate, all of which supports brain energy needs. Astrocytic glycogen breaks down to lactate against hypoglycemic neural

injury. Studies have shown that the activities of key glycolytic enzymes in the brains of patients with AD are changed, including a significant increase of pyruvate kinase and lactate dehydrogenase in frontal and temporal cortex, and a significant decrease of glucose 6-phosphate dehydrogenase activity in hippocampus [50, 51]. Furthermore, some glycolytic enzyme activities are correlated with contents of lactate dehydrogenase and glial fibrillary acidic protein (GFAP) in astrocytes, implicating that the increased activity of some glycolytic enzymes may be the result of astrocytic dysfunction developed in the course of AD [50]. AD is also linked to aerobic glycolysis whereby glucose does not go into oxidative phosphorylation in astrocytes. Indeed, it is found that the spatial distribution of aerobic glycolysis correlates spatially with A $\beta$  deposition [52].

#### 4. Metabolic dysfunction from astrocytes: a trigger for A $\beta$ pathology

Although the brain is about 2% of the whole body weight, it consumes about 15% of the cardiac output, 20% of the oxygen, and 25% of the glucose to maintain cerebral functions. Therefore, the brain is such an organ with the highest energy requirements in the human body. It is well-known that astrocyte, as the most important energy regulator in the brain, maintains brain homeostasis and restores ion gradients such as post-synaptic and action potentials, as well as uptake and recycling of neurotransmitters, which all count toward energy consumption in the brain.

The generation and deposition of A $\beta$  in the brain is a conventional molecular trend in the pathogenesis of AD. So far the amyloid hypothesis of AD has been recognized as the main pathological features. Therefore, not surprisingly, compelling studies have supported the notion that metabolic dysfunction of astrocyte is a trigger for A $\beta$  pathology [53, 54] given the importance of astrocytes in the brain.

##### 4.1 Brain homeostasis disorders induced by astrocytic dysfunction: a contributor to A $\beta$ pathology

Increasing evidence has indicated that astrocytes, the most abundant cells in the brain, plays a pivotal role in maintenance of brain extracellular homeostasis and functional recovery from injuries through a variety of means, including regulating intracellular ion homeostasis [55], providing a metabolic support for brain energy [55], regulating metabolism of neurotransmitters, maintaining the structure and function of BBB, clearing the abnormal aggregates in the brain, and regulating the brain immune response and neurodevelopmental processes [56-58]. Astrocytic dysfunction induces and facilitates neurodegeneration, which leads to cognitive impairment found in neurodegenerative diseases, such as AD, Parkinson's disease [59] and Huntington disease [60, 61]. Therefore, it is thought that brain homeostasis disorders induced by astrocytic dysfunction are closely associated with AD.

Brain homeostasis failure leads to an inability to maintain brain physiological balance that causes severe maladjustment [62, 63]. During aging, the capabilities of brain homeostasis are increasingly vulnerable as evidenced by age-related Alzheimer's disease [64, 65]. Therefore, numerous studies have demonstrated that failure in brain homeostasis enhances A $\beta$  deposition and a decline in A $\beta$  clearance. The past several decades have witnessed many important discoveries that provide novel insights into associations between amyloid plaques and perturbed astrocytic homeostasis [10, 55, 65]. Impaired cellular ion homeostasis and energy metabolism not only are triggers for A $\beta$  deposition and a decline in A $\beta$  clearance, but also render neurons vulnerable to A $\beta$  excitotoxicity [66]. It is also known that presenilin mutations perturb calcium homeostasis in astrocytic endoplasmic reticulum, indicating that aberrant calcium homeostasis is linked to altered APP processing [67].

## 4.2 Oxidative stress and neuroinflammation induced by metabolic dysfunction from astrocytes: a contributor to A $\beta$ pathology

Increasing evidence demonstrates that neuroinflammation and oxidative stress occur throughout the pathological process of AD [68-70]. An important pathological feature of AD is that oxidative stress triggers an active and self-perpetuating cycle of chronic neuroinflammation, which further promotes oxidative stress that eventually leads to irreversible neuronal dysfunction and cell death [69, 71, 72]. Evidence has also indicated that not only oxidative stress and neuroinflammation have a close association with A $\beta$  pathology, but also the interaction between oxidative stress and neuroinflammation enlarges A $\beta$  generation [71, 73].

It is known that senescent astrocytes may link advanced age with increased risk for sporadic AD [65, 74]. It is also known that astrocytes, as a site for the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), are the initiator of oxidative stress that occurs through the whole process of AD pathogenesis [65]. Compelling evidence has also demonstrated that the inflammatory reaction and oxidative stress are generated by activated astrocytes and/or senescent astrocytes that produce a number of inflammatory cytokines including interleukin-6 (IL-6) and IL-1 [65, 74, 75]. Astrocytic metabolic phenotype modified by proinflammatory cytokines is observed in AD while long-term treatment with IL-1 $\beta$  or TNF- $\alpha$  alone enhances glucose utilization in astrocytes [11]. Given that energy failure, increased oxidative stress, and neuroinflammation are critical for A $\beta$  pathology [76, 77], astrocytic metabolism dysfunction may dictate the occurrence of A $\beta$ -related events through mechanisms that are yet to be elucidated.

## 4.3 Proteolytic processing of APP regulated by metabolic dysfunction from astrocytes

**Proteolytic processing of APP**—Amyloid precursor protein (APP), an integral membrane protein, is best known as the A $\beta$  precursor molecule. Proteolytic processing of APP commonly includes an amyloidogenic and a non-amyloidogenic pathway. In the amyloidogenic pathway A $\beta$  is generated by the sequential proteolysis of two enzymes:  $\beta$ -secretase and  $\gamma$ -secretase [78]. The non-amyloidogenic pathway is a process whereby  $\alpha$ -secretase cleaves APP in the extracellular domain and releases soluble APP $\alpha$ . Following this cleavage, the C-terminal fragment ( $\alpha$ -CTF) is cleaved again by  $\gamma$ -secretase to yield 3kDa fragment known as P3.

**$\alpha$ -secretase**—APP can be cleaved by  $\alpha$ -secretase within the APP domain between Lys687 and Leu688, producing a soluble  $\alpha$ -APP domain and the C-terminal fragments containing C83. C83 can then be cleaved by  $\gamma$ -secretase at residue 711 or 713 to release a P3 fragment. This process does not yield A $\beta$  peptide [79]. Hence, the  $\alpha$ -secretase pathway has a beneficial effect in lowering A $\beta$  peptide levels. Considerable evidence has demonstrated that abnormal astrocytes play a crucial role in A $\beta$  generation and deposition. The production and aggregation of A $\beta$  is regulated by abnormal astrocytes via interfering with APP cleavage. A recent study has discovered that a group of high-energy compounds (HECs), including ATP, GTP, CTP, phosphocreatine, phosphoenol pyruvate, S-adenosylmethionine and acetyl coenzyme A, promotes APP  $\alpha$ -secretase-processing with varying potencies whereas their cognate counterparts do not have the same effects that could be eliminated by energy inhibitors [80]. Yao et al [81] have also shown that 2-deoxy-D-glucose (2-DG) increases  $\alpha$ -secretase and decreases  $\gamma$ -secretase expression via inducing ketogenesis and sustaining mitochondrial function, and reduces pathology in female mouse model of AD. These findings implicate that improving astrocytic energy supply may be useful in slowing down the progression of AD via enhancing  $\alpha$ -secretase-processing.

**$\beta$ -secretase**—A large body of evidence supports that  $\beta$ -secretase (beta-site amyloid precursor protein-cleaving enzyme 1, BACE1) is the rate-limiting enzyme for the production of  $A\beta$  [82, 83]. In APP transgenic (Tg2576) mice, energy inhibition by several pharmacological agents (insulin, kainic acid, 2-deoxyglucose and 3-nitropropionic acid) caused approximately a 150% increase in cerebral BACE1 levels and a 200% increase in cerebral  $A\beta_{40}$  levels, respectively, when compared with controls, implicating that impaired energy production in the brain may enhance  $A\beta$  pathology by elevating BACE1 levels and activities [84]. In addition, bioenergy impairment could also contribute to neuronal apoptosis and elevated  $\beta$ -secretase, thereby promoting AD pathogenesis [85]. It is obvious that bioenergy impairment of astrocytes would be a decisive factor in  $A\beta$  generation owing to elevated  $\beta$ -secretase levels and activities.

**$\gamma$ -secretase**— $\gamma$ -secretase is a multi-subunit protease complex that consists of four individual proteins: presenilin (PS1 or PS2), nicastrin, APH-1 (anterior pharynx-defective 1, APH-1 $\alpha$  or APH-1 $\beta$ ), and PEN-2 (presenilin enhancer 2). As described above, improving astrocytic energy supply by 2-DG lowers  $\gamma$ -secretase level and limits  $A\beta$  pathogenesis *in vivo* [81]. On the contrary, activated astrocytes have an increased expression of the  $\gamma$ -secretase components presenilin-1 and nicastrin [86]. Hence, a hypothesis has been postulated that astrocytic bioenergy impairment triggers  $\gamma$ -secretase overexpression and contributes to  $A\beta$  pathogenesis.

#### 4.4 Post-translational modification of APP by metabolic dysfunction from astrocytes ?

Besides many types of proteolytic processing, APP undergoes extensive post-translational modifications including glycosylation, phosphorylation, and tyrosine sulfation [87]. Protein glycosylation, common in Eukaryotic proteins, is the most important and complex form of post-translational modifications. APP contains both *N*-linked and *O*-linked sugars [88, 89]. *N*-linked glycosylations are covalently attached to Asn residues within a consensus sequence (Asn-Xaa-Ser/Thr), enabling prediction of the modification sites and sharing of a common pentasaccharide core (GlcNAc<sub>2</sub>Man<sub>3</sub>) recognized by *N*-glycanase enzymes. Mucin-type, the most prevalent *O*-linked glycosylation is characterized by an *N*-acetylgalactosamine (GalNAc) residue linked to the hydroxyl group of Ser or Thr. GalNAc residue is installed by a family of 24 *N*-acetyl-galactosaminyltransferases, and further elaborated by a series of glycosyltransferases to generate higher *O*-linked structures. It has been identified that the structures of the core type *O*-linked glycans are attached at the residues Thr291, Thr292 and Thr576 of the full-length APP695 with the use of electron transfer dissociation and collision [90]. Griffith et al. [91] first presented that APP is modified with *O*-linked *N*-acetylglucosamine, namely *O*-linked to cytoplasmic serine or threonine residues (*O*-GlcNAc). Numerous results support that the post-translational modification of APP by glycosylation is a key event in determining the processing of the protein [92-94].

Phosphorylation of APP is known to occur on several phosphorylatable amino acid residues in its cytoplasmic and luminal region [95, 96]. It has been found that phosphorylation of APP at Thr668 induces neurodegeneration via regulating the nuclear translocation of the APP intracellular domain [97] while Thr668 phosphorylation may facilitate the BACE1 cleavage of APP to increase  $A\beta$  generation [98].

It is also well known that APP is a type I transmembrane protein with a large ectodomain. It is found that APP can undergo sulfation on tyrosine residues within its ectodomain [87]. Furthermore, sulfation is shown to be critical for the effect of heparin on APP processing and  $A\beta$  production [17].

Additionally, a number of post-translational modifications to APP have been found in the brains of AD patients and transgenic animal models of AD. As metabolic disorder is an important determinant for post-translational modifications [99-103], a reasonable conclusion is that metabolic disorder will influence AD-associated APP post-translational modifications. However, whether an astrocytic metabolism disorder promotes AD-associated APP post-translational modifications remain unknown. Hence, identification of APP post-translational modifications promoted by astrocytic dysfunction may provide novel therapeutic targets for AD treatment.

#### 4.5 Astrocytes, metabolic disorder and failure of A $\beta$ clearance

Emerging evidence suggests that failure of A $\beta$  clearance in the brain is an important factor in the progression of AD [104]. Multiple cellular and molecular mechanisms have been elucidated that astrocytes are involved in A $\beta$  clearance. Within the progress of A $\beta$  deposition and pathological severity, the ability of astrocytes to clear A $\beta$  is gradually compromised under a cytokine cycle of molecular and cellular cascades induced by astrocytic activation, microglial activation, and A $\beta$  deposition, which all confer risks for AD. It has been recognized that astrocytes can lose energy-generating reactions to clear aggregated proteins when astrocytes show persistent response to the chronic inflammation and oxidative stress induced by microglial activation and/or A $\beta$  deposition [105-107]. Thus, the cytokine cycle of molecular and cellular cascades from astrocytic activation, microglial activation and A $\beta$  deposition may be one of the most important factors in A $\beta$  clearance [108-110].

Astrocytes play many pathophysiological roles, such as biochemical support of endothelial cells that form the BBB, nutrient supply for the nervous tissue, maintenance of ion homeostasis, as well as clearance and degradation of aggregated proteins. Various studies implicate that the BBB plays a role in the deposition of A $\beta$  and faulty clearance of A $\beta$  from the brain [111-113]. Astrocytic BBB disruption is a critical contributor to the failure of A $\beta$  clearance whereas the astrocyte end-feet encircling endothelial cells are in the maintenance of the structural and functional integrity for BBB [114-116]. As the main function of BBB regulates the passage of molecules and leukocytes in and out of the brain, BBB injury by astrocytic disorder would be a major underlying cause of neurodegenerative disorders since astrocytic-endothelial tight junctions disrupt the integrity of the BBB [117-119]. Therefore, the main pathogenesis of AD involves disruption of BBB that subsequently not only delays the A $\beta$  clearance from the brain but also facilitates an increase in A $\beta$  influx from the cerebrospinal fluid (CSF). Metabolic dysfunction of astrocytes may perturb the rapid clearance of A $\beta$  across the BBB via increasing levels of receptor for advanced glycation end products (RAGE) [120-122], downregulating low density lipoprotein receptor-related protein 1 (LRP-1) [123, 124], and dysregulating enzymatic degradation (such as matrix metalloproteinases, MMPs) [125]. Furthermore, oxidative stress and neuroinflammation may be critical mediators between A $\beta$  clearance and astrocytic metabolic dysfunction (Figure 1).

## 5. Conclusion and perspective

Increasing evidence supports the notion that impaired brain glucose metabolism is closely associated with abnormal astrocytic function in AD. Oxidative stress and neuroinflammation induced by metabolic dysfunction of astrocyte likely contribute to A $\beta$  pathology. Specifically, metabolic dysfunction of astrocyte may: 1) regulate proteolytic processing of APP; 2) modulate APP post-translational modification; 3) lead to the failure of A $\beta$  clearance; 4) cause AD indirectly by interacting with many other pathologic processes. However, a few studies also demonstrated that metabolic dysfunction of astrocytes could have neuroprotective properties that did not exhibit detrimental outcomes [9, 72, 111, 130, 131]. Therefore, the exact role of astrocytic metabolic dysfunction in A $\beta$  pathology remains

unclear at this time. Clinically, it is also unclear whether metabolic dysfunction of astrocytes would be indeed beneficial in AD intervention. Thus, it is necessary to further understand the mechanisms of metabolic dysfunction of astrocytes before it can be targeted for AD prevention and treatment.

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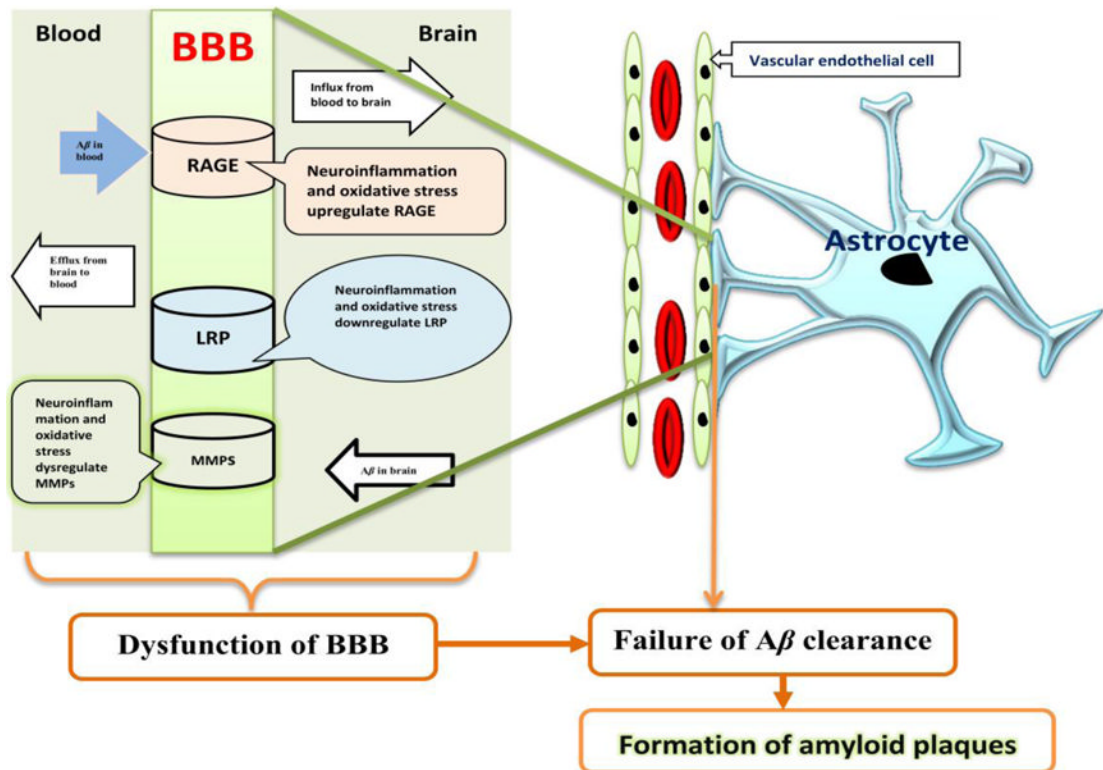
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**Figure 1. Schematic diagram of failure of  $A\beta$  clearance by metabolic dysfunction from astrocyte** Metabolic dysfunction from astrocyte leads to failure of  $A\beta$  clearance by disrupting BBB transporter. Metabolic dysfunction from astrocyte may injury its rapid clearance across the BBB via increasing RAGE level, downregulating LRP-1, and dysregulating enzymatic degradation (such as MMPs). RAGE is a member of multi-ligand immunoglobulin superfamily and cell surface receptor. RAGE promotes influx of circulating  $A\beta$  across the BBB from blood to brain, which is antagonized by LRP-1-mediated efflux of  $A\beta$  [126, 127]. LRP-1, a multifunctional scavenger and signaling receptor belonging to the low-density lipoprotein receptor family, plays a role in the cellular transport of cholesterol, endocytosis of diverse ligands, transcytosis of ligands across the BBB [124, 128]. LRP-1, abundantly expressed in capillary endothelial cells, is a major clearance receptor responsible for efflux of  $A\beta$  from brain to blood [123, 124]. MMPs are involved in BBB damage related to  $A\beta$  clearance [125] and formation of  $A\beta$  plaques [129]. Neuro-inflammation and oxidative stress may a critical mediator between  $A\beta$  clearance and metabolic dysfunction from astrocyte.