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Review Article

L-Arginine and Alzheimer's Disease

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Abstract: Alzheimer's disease (AD), the most common form of dementia, is characterized by progressive neurodegeneration and loss of cognitive and memory functions. Although the exact causes of AD are still unclear, evidence suggests that atherosclerosis, redox stress, inflammation, neurotransmitter dysregulation, and impaired brain energy metabolism may all be associated with AD pathogenesis. Herein, we explore a possible role for L-arginine (L-arg) in AD, taking into consideration known functions for L-arg in atherosclerosis, redox stress and the inflammatory process, regulation of synaptic plasticity and neurogenesis, and modulation of glucose metabolism and insulin activity. L-arg, a precursor of nitric oxide and polyamine, exhibits multiple functions in human health and may play a prominent role in age-related degenerative diseases such as AD.
Key Words: L-arginine; nitric oxide synthase; nitric oxide; arginase; polyamines; neurogenesis, stem cells, Alzheimer's disease

Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disease with an insidious onset, characterized by memory impairment and cognitive disturbances that become increasingly more severe with disease progression. It is a debilitating and dehumanizing illness, inflicting immense suffering on its victims and their families, and on society. Approximately 4.5 million Americans are currently affected by AD [1]. However, if there are no effective strategies to treat or prevent AD [2], it is projected to affect up to 9 million people by 2040 as the elderly population grows.

The neuropathology of AD is characterized by senile plaques, neurofibrillary tangles (NFT), and, neuronal loss [3-6]. Although the exact causes of AD are still unknown, studies suggest that the genesis of sporadic AD is associated with atherosclerosis, redox stress, inflammatory processes, and/or abnormal neurotransmission and brain glucose metabolism. Current treatment strategies are limited to altering cholinergic and NMDA neurotransmission and show only modest efficacy. No treatments are currently available to target the underlying mechanism of the disease.

L-arginine (L-arg) is a semi-essential, proteinogenic amino acid [7] that was discovered in mammalian protein by Hedin in 1895 [8], and since 1886 it has been recognized as a naturally occurring molecule [9]. It is involved in two major metabolic pathways as showed in **Figure 1**. One of them is the nitric oxide synthase (NOS) pathway where L-arg is converted to NO and L-citruline [10, 11]. The other pathway is the arginase pathway that will be discussed further below.

There are three isoforms of NOS that have been discovered so far. They are named according to the cell types from which they were first isolated: neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NOS (eNOS) [10, 12]. These NOSs have different functions [10-13]. The expression of nNOS and eNOS are constitutive and regulated by

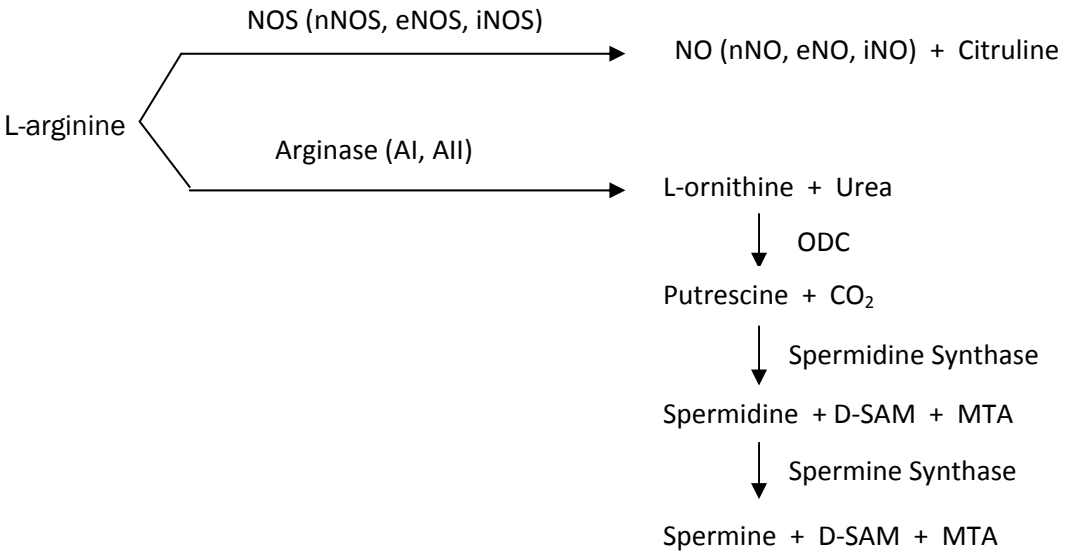

Figure 1 The major two metabolic pathways of L-arginine. ODC, ornithine decarboxylase; D-SAM, decarboxylase SAM; MAT, methylthioadenosine.

calcium/calmodulin. Neuronal NO (nNO) and endothelial NO (eNO) are produced at low rates by nNOS and eNOS, respectively [14]. The relationship of L-arg to the isoforms of NOS is intricate. Noticeably, the intracellular L-arg concentration (about 1-2 mM), taken up and maintained by endothelial cells through the transport system, is so much higher than the K_m value of purified eNOS (≈ 2.9 μmol/L) that eNO should not be increased further by addition of extracellular L-arg. However, the "L-arginine paradox" that synthesis of eNO can be enhanced as a response in a concentration-dependent manner to the increase of extracellular L-arg concentration has been observed [13, 15]. This reaction plays a crucial role in the vascular homeostasis associated with L-arg [16]. In terms of iNOS, its expression is induced in inflammatory cell types by cytokine stimulation, and its activity is independent of calcium, and production rate of inducible NO (iNO) is high [17].

L-arg and NO affect the cardiovascular system as endogenous antiatherogenic molecules that protect the endothelium, modulate vasodilatation, and interact with the vascular wall and circulating blood cells [18-22]. Together, they can function in the brain as noradrenergic, noncholinergic neuro-transmitters in learning and memory, synaptic plasticity, and neuroprotection [23, 24]. They can influence the immune system too by playing a key role in regulating inflammatory processes [25] and redox stress. They can also modulate the metabolism of glucose and insulin activity as natural constituents from diets [26] and regulate neurogenesis. Since L-arg and its product, NO, exert such a range of critical roles in regulating physiological functions of brain and other organs, we hypothesize that L-arg can possibly affect the AD pathogenesis. The other metabolic pathway that involves L-arg is the arginase pathway where L-arg is broken down into urea and L-ornithine and genesis of polyamines including putrescine, spermidine, and spermine [27, 28]. Two isoforms of arginase (AI and AII) [29] were discovered in 1973 [30, 31], identified positively in 1983 [32], and confirmed subsequently in 1989 [33]. They are encoded by different genes, distributed in different tissues, cell types and intracellular locations, and, have different biochemical properties [28, 34, 35]. AI, called liver-type arginase, was first found as a component of the urea cycle. It is expressed at high level in livers as a cytosolic enzyme and at a low level in central nerve system (CNS). It is also induced to express at a high level when exposed to multiple cytokines and factors in various tissues and cells [28, 34-36]. AII is called kidney-type arginase and is expressed at a low level in the mitochondrion, and it too can be induced by cytokines. Like AI, it is also expressed in the germinal zones, hippocampus, spinal, and

other motor neurons of mice [37, 38]. Loss of AI leads to potentially fatal hyperammonemia and hyperargininemia, states characterized by a series of stereotypic clinical disorders such as growth retardation, increased mental impairment, and spasticity [39-40]. However, these symptoms can be partially attenuated through enhancing the expression and activity of AII to compensate for the deficiency of AI [41-44]. Based on the distribution and expression of these isoforms, we postulate that AI and AII might participate in many physiological processes, including inflammation, neurogenesis and apoptosis.

Polyamines are the major products of L-arg metabolized by arginase. Ornithine acts as a starting substrate to be converted into putrescine, spermidine and spermine. There are three main polyamines that can be identified with their different lengths of carbon chains [45, 46]. They act as variably functional molecules that are essential for cell regeneration, tissue growth, and development [47-51].

In this review, we explore a possible role for L-arg in AD, taking into consideration the known functions of L-arg in atherosclerosis, oxidative stress and the inflammatory process, regulation of synaptic plasticity and neurogenesis, and modulation of glucose metabolism and insulin activity.

The Possible Effects of L-Arg on AD via Anti-atherosclerosis

The Relationship between AD and Atherosclerosis

Increasing evidence suggests a strong relationship between AD and atherosclerosis. Indeed, some investigators have proposed that AD is a primary neurovascular disease [52].

First, AD and atherosclerosis have many risk factors in common [53-55]. Numerous studies have shown that established risk factors for vascular disease, including diabetes mellitus, smoking, and atherosclerosis, also predispose individuals to AD [56-61].

Second, autopsy series have provided evidence of links between atherosclerosis and AD [62, 63]. Seward *et al* found that the atherosclerotic lesions and the degree of stenosis of Circle of Willis are significantly more severe in AD brains than in age-matched controls. Additionally, the index of stenosis apparently relates to the total plaque score, neuritic plaque score, NFT score, Braak stage score, and white matter rarefaction score, all of which are measures for AD neuropathological lesion [62]. Beach *et al* also reported that increase in the atherosclerotic grade increased the odds ratios for the diagnoses of AD and vascular dementia (VaD) [63]. Furthermore, studies suggest that the possible mechanism through which atherosclerosis influences the development of AD is hypoperfusion in the brain [62, 63]. Additionally, based on previous points, Torre *et al* and other researchers found it possible to clinically diagnose AD earlier through neuroimaging techniques such as single-photon emission computed tomography (SPECT) because the presence of microvascular abnormalities precedes cognitive impairment and neurodegeneration [52, 64, 65, 66]. Hirao *et al* reported that subjects with reduced regional cerebral blood flow in the bilateral temporo-parietal areas and the precunei will finally become AD cases [67].

Third, some studies have shown that treatment of atherosclerosis may also benefit AD. Sparks *et al* suggested that administration of atorvastatin to patients with AD may attenuate cognitive decline and generally slow down the progression of mild-to-moderate AD [68]. That study agrees with others in which statins were used as the treatment for AD [69-71]. Petanceska *et al* even found that administration of atorvastatin can significantly reduce Aβ amyloid deposition in an animal model [72].

In summary, increasing evidence suggests that atherosclerosis is associated with the AD progression. Interdicting atherosclerosis might therefore delay the onset or slow the progression of AD.

L-Arg Affects AD via Anti-atherosclerosis

L-arg exerts its function in the cardiovascular system mainly through the increase of NO production [73-75]. Lack of L-arg in vascular endothelium may result in the deficiency of NO [16], a key feature in the development of atherosclerosis (18). Thus, abnormalities in L-arg availability and metabolism are proposed in the pathogenesis of atherosclerosis, especially in hypercholesterolemia [76].

Creager *et al* discovered that forearm vasodilatation is markedly improved through administration of L-arg in an endothelium-dependent manner [77]. Similar results were seen in other studies [78, 79]. In fact, the effect is more profound than that observed after lipid-lowering therapy [80-82]. Other studies obtained parallel results in patients with hypercholesterolemia [78, 83]. From previous studies, hypercholesterolemia as a risk factor of atherosclerosis is well known to cause early endothelial dysfunction, abnormal interactions between vascular cells, platelets and monocytes [84, 85], and disability of L-arg [76]. However, extra dietary supplements of L-arg may decrease platelet aggregation [82, 86] and mononuclear cell adhesiveness in hypercholesterolemic patients [87, 88]. Furthermore, thiobarbituric acid reactive substances (a marker of lipid peroxidation) are decreased after L-arg infusion in hypercholesterolemic subjects [89]. Recent studies showed that chronic oral supplementation with L-arg may block the progression of atherosclerotic plaques via restoration of NOS substrate availability and decrease of vascular stress [90, 91].

Hypertension, an established risk factor for atherosclerosis is strongly associated with AD [92, 93]. Therefore, through its effect on hypertension, L-arg may affect AD. Siani *et al* reported that oral administration of L-arg as an enriched diet in healthy volunteers caused a reduction in arterial blood pressure [94]. Rector *et al* showed that arterial blood pressure dropped in patients with heart failure after treatment with L-arg [95]. The study also reported that acutely oral L-arg improves brachial artery flow-mediated dilation in patients with essential hypertension [78].

Cigarette smoking, another salient risk factor for atherosclerosis may also be affected by L-arg and be linked to AD. An association between smoking and an increased risk of dementia has been reported [59, 96, 97], although not always [98, 99, 100]. Smoking raises oxidative stress to degenerate NO through increasing oxygen-derived free radicals and lipid peroxides [101]. It also accelerates monocyte adhesion and the vulnerability of low density lipoprotein (LDL) to be oxidized [102]. L-arg can affect atherosclerosis through attenuating the effects of smoking. Using treatment with extra L-arg, Adams *et al* reported that adhesion of monocyte and endothelial cells and the expression of intercellular adhesion molecule in endothelial cells are decreased [103]. Other studies also showed that the microcirculation is improved by L-arg supplementation in smokers [76, 104, 105].

The mechanisms through which L-arg affects atherosclerosis are not fully understood, and a number of possible mechanisms have been proposed, including the "L-arginine paradox". Excess L-arg can enhance NOS activity through NO production, especially when battling with the deficiency of eNO in the presences of LDL cholesterol [106], by acting as (i) a relaxing factor in the regulation of vasodilatation [107]; (ii) an inhibitor to attenuate platelet aggregation [108], and monocyte and leukocyte adhesion [109]; (iii) an inhibitor to depress the proliferation of smooth muscle cells [110]; and (iv) reducer of vascular oxidative stress and the expression of redox-regulated genes [111]. It is worth mentioning that only eNO is helpful to anti-atherosclerosis, whereas iNO accelerates atherogenesis through synthesis of the cytotoxic NOO^- radical [112]. Further, exertion of its function by L-arg upon the cardiovascular system is concentration-dependent. At lower plasma concentrations, L-arg can selectively improve endothelial function so that patients with elevated asymmetric dimethylarginine (ADMA) levels have diminished NOS activity; at middle concentration levels, it can perform direct vasodilatation through the endocrine effects of secreting insulin and growth hormone; at higher concentration levels, it can produce vasculature unspecific vasodilatation [113]. Moreover, chronic supplement of L-arg may have anti-hypertensive effect through the reduction of renal vascular resistance and the depression of angiotensin-converting enzyme [114, 115].

In conclusion, L-arg has multiple direct and indirect effects on human vasculature, and might play an important role in the pathogenesis of both atherosclerosis and AD.

L-Arg, as a Precursor of NO, Affects AD via Influencing Oxidative Stress

The Relationship between AD Pathology and Brain Oxidative Stress

Brain oxidative damage is prevalent in AD due to high cerebral energy demand and oxygen

consumption that are required for brain functions and possible failure of brain antioxidant defenses [116]. Numerous experimental data, as indicated by different markers for oxidative damage of DNA, protein, lipid and glucose, shows that oxidative stress plays an important role in AD pathogenesis, and is highly associated with brain Aβ amyloidosis [117-123]. Much experimental evidence also implies that increased oxidative damage may not just be the consequence but a primary cause of AD pathogenesis [124]. Indeed, Aβ amyloidogenesis promotes generation of free radicals, oxidative damages, and inflammation in AD brain [125].

In summary, oxidative stress contributes to the progress of AD and there may be a vicious cycle between brain oxidative stress and Alzheimer's Aβ amyloidogenesis.

L-Arg Affects AD via Influencing Oxidative Stress

NO derived from L-arg is a potential source of redox stress. It can be quickly cleared through reacting with superoxide (O_2^-) to generate peroxynitrite ($ONOO^-$) with a half-life of <1 sec while cells are in a pro-oxidative state. As a highly reactive species, $ONOO^-$ can react via homolytic or heterolytic cleavage and, generate secondary constituents of nitroxidative stress and highly reactive oxygen/nitrogen species (ROS/RNS) including NO_2^+, NO_2, and OH radical. The high nitroxidative stress acts to initiate the redox reaction, thereby inducing apoptosis and overall damage to neurons and endothelial cells [126]. The toxic constituents that are generated from the reaction of NO under oxidative stress are the property of a family called "reactive nitrogen oxidative species (RNOS)," of which peroxynitrite and nitrogen oxide are the main constituents [127, 128]. Furthermore, the term "nitroxdative stress" has been used to indicate the cellular damage that is elicited by excess NO and RNOS [129, 130]. Wang *et al* supported these assertions when they reported neuronal apoptosis induced in a concentration- and time-dependent manner while $ONOO^-$ increased, H_2O_2 rapidly decayed, and ROS slowly decreased [131]. Other studies also suggest that NO and ROS are involved in the pathogenesis of AD by synergistically inducing neuronal damage and death [127, 132, 133].

In contrast, David *et al* drew a totally opposite conclusion reporting that NO provided protection against ROS by way of cell culture [134, 135]. They also found that neurons expressing NOS survived under ischemia reperfusion, whereas neurons surrounding the ischemia area and not expressing NOS died [136]. The possible mechanism that NO can attenuate the toxic effects of ROS might be that NO can directly react with O_2^- to form $ONOO^-$, thereby rapidly rearranging nitrate at physiological pH 4.0 before it interacts with cells [135].

Whether NO is neuroprotective or neurotoxic also depends on the different functions of its isoforms, the stage of treatment with corrective drugs [137], the local concentration of NO, especially at different ischemia stages [138, 139], and the concentration of ROS [140]. Glebov *et al* used L-arg and its inhibitor by intravenous injection separately after inducing oxidative stress in rats. They found that iNOS inhibitor improves antioxidant protection, whereas L-arg and the nonselective inhibitor do not [141]. They further suggested that iNO produced by iNOS enhances oxidative stress. Another study showed that NOS activities and the expression of markers for oxidative stress are increased in cell culture and that the use of nNOS inhibitor cannot rescue the cells from dying [142]. The finding suggested that nNOS might not be toxic. It was also reported that iNOS is a mediator of neuroprotection induced by preconditioning with oxidative stress such as H_2O_2 at low concentration in a cell culture [140].

In addition, some studies showed that ischemia/reperfusion in the brain possibly causes AD [143, 144]. L-arg can protect it through exerting its anti-oxidant functions. If lacking L-arg and NO, the brain would have an increase of superoxide anion formation [147]. Administration of L-arg may be associated with the antiradical and antioxidant effects of NO, inhibiting the effects of inositol-1,2,5-triphophates, and inhibiting the accumulation of leukocytes in the reperfused tissue [145, 146]. Maksimovich *et al* suggested that the antioxidant property of L-arg in brain ischemia/reperfusion might be because of activation of NO synthesis, involving eNOS which acts as a radical trap, and facilitating the removal of radical and reductions in their toxicity [148]. However, inhibiting the activity of nNOS and iNOS resulted in improvements in

brain circulation and reduction of the ischemic zone [149]. eNO affects vessel walls by inhibition of lipoxygenase-dependent lipid and lipoprotein oxidation [147, 150]. Further, it affects vessels by its ability to enhance the perfusion of brain tissues via NO-dependent dilation of vessels [151], and neurons by suppression of the N-methyl-D-aspartate (NMDA) receptor activity [150, 152]. Also, eNO affects the prooxidant-antioxidant equilibrium by inducing a shift associated not only with its potentially high levels that can react with the multitude of target molecules responsible for the development of oxidative stress, but also with its decrease to contributions of other factors to the antioxidant potential of the body, especially changes in the oxygen affinity of hemoglobin [153].

Even in patients with hyperlipidemia-hyperglycemia, administration of L-arg can decrease the oxidative stress [154]. Supplementation with L-arg improves oxidative stress by inducing postprandial hypertriglyceridemia [155-157], preventing the depletion of serum plasma glutathione peroxidase that is a serum antioxidant enzyme, and preventing endothelial dysfunction [157, 158].

In conclusion, L-arg and NO can have a dual role in AD under oxidative stress. Their neuroprotective or neurotoxic roles are limited by isoforms and the concentration of ROS.

The Effects of L-Arg on AD via Influencing Inflammation

The Relationship between AD and Inflammation

Increasing evidence shows that chronic inflammatory processes of the central nervous system (CNS) are neurotoxic and may contribute to AD pathogenesis [159]. For example, during inflammation, elevated pentraxins, increased pro-inflammatory cytokines, chemokine alterations and microglial activation trigger functional impairment and structural damage to the CNS [160].

On the other hand, Aβ as a central mediator in AD pathogenesis [161, 162] may also promote neurodegeneration by inducing the activation of microglial cells and astrocytes. The induction results in the acceleration of inflammation through releasing various inflammatory mediators [163, 164]. In addition, some epidemiological studies strongly support that non-steroidal anti-inflammatory agents may have therapeutic value in AD [165-168]. We conclude that there is a great potential that improvement in the immune system may prevent CNS inflammation, and hence, AD pathology.

L-Arg Regulates Inflammation

Over the last two decades, increasing evidence suggests that L-arg plays important roles in immunological processes.

L-arg is a potent modulator of immune cell functioning [25]. Kirk *et al* fed mice with 1% arginine HCL and found an increase in thymic weight due to increased number of total thymic T lymphocytes [169]. In the athymic mice, arginine supplementation increased the total number of T cells and, amplified delayed-type hypersensitivity responses. In humans, dietary supplementation has been shown to enhance T-cell-mediated function and speed up wound healing by increasing reparative collagen synthesis [170].

The ability of L-arg to regulate immune cell-mediated function depends on its concentration. Albina *et al* found that low concentrations of L-Arg (<0.1 mM) in culture media enhance activation-associated functions in rat resident peritoneal macrophages, including cytotoxicity against tumor cells, superoxide production, and phagocytosis. On the contrary, higher concentrations of L-arg (about 0.1 mM to 1.2 mM) suppress superoxide production, cytotoxicity, phagocytosis and protein synthesis. They also revealed that low concentrations of L-arg enhance phagocytosis probably due to macrophage-derived arginase activity. Probably due to NO^- production induced by L-arg/NO pathway [171, 172], higher, non-physiological concentrations of L-arg produce more prominent decreases of phagocytic activity compared with controls - a result that agrees with Potenza *et al* [25]. In summary, L-arg can be a modulator regulating inflammation.

The Effect of L-Arg and NO on AD via Influencing Inflammation

Scott *et al* used L-arg to revise free radical

production and the development of experimental allergic encephalomyelitis (EAE) in a rat model. They found that L-arg can suppress the development of neurological symptoms and the formation of inflammatory lesions in the CNS of diseased animals, eventually efficiently delaying disease onset. They also found that superoxide and hydrogen peroxide are markedly decreased and the level of nitrite, a breakdown of NO formation, is significantly increased in the CNS [173]. In conclusion, they recommended L-arg is a protective molecule, modulating oxidant-mediated neuroinflammation by the production of NO [173]. However, other studies reported that iNO's effect on neurons contributed to neurodegenerative disease [174, 175]. Vodovotz *et al* found that NFT-bearing neurons express iNOS in the brain regions influenced by AD [176]. Others found that nitrotyrosine staining is increased in AD brains tissue [177]. Still other studies suggested that high generation of iNO may contribute to pathogenesis in AD due to sustained exposure and oxidative damage by peroxynitrite - an intermediate iNO reaction product [143, 144]. These results agreed with a prior study [178]. In addition, iNO, as a free radical, activated cyclooxygenase II (COX-2) that in turn activated the arachidonic acid cascade that is known to be pro-inflammatory [179, 180]. All in all, these findings seem to suggest that overproduction of iNO is harmful by inducing the inflammatory process and possibly AD. The discrepancies about the role of NO under oxidative stress have already been elaborated above.

In conclusion, L-arg and NO, as modulators, may play a role in AD by influencing inflammatory processes. Regulating the level and the metabolic pathway of L-arg, and selectively producing different isoforms of NO may produce therapeutic effects. Further investigations are necessary, however, to confirm or comprehend these effects and potentials.

The Effect of L-Arg on AD through Production of the Neurotransmitter NO

NO is a Neurotransmitter

The first evidence that NO acts as a neurotransmitter is reported by Garthwaite *et al*. They showed that stimulation of cerebellar NMDA receptors by glutamate releases NO [181] that then acts as a neurotransmitter in CNS to regulate the synaptic plasticity involved in cognitive processes, memory, long-term potentiation (LTP) and long-term depression (LTD) [182]. Some evidence has shown that NO, produced presynaptically or in interneurons postsynaptically, acts during cerebellar and striatal LTD. On the other hand, the postsynaptic generation of NO presynaptically acts in hippocampal and cortical LTP [183]. Furthermore, Thomas *et al* found that NO, as a transmitter, modulated synaptic efficacy at the neuromuscular junction. They also demonstrated that NO regulates transmitter release and adenosine-induced depression via a cGMP-dependent mechanism which occurs after Ca^{2+} entry [184-186]. The results agree with Nickels *et al* [187].

The Effects of NO on AD

Since it was found immunohistochemically in rats [151] that NO and neurons are strongly linked via localized NOS protein, researchers supposed that NO as a transmitter is related with AD. Thus, they started further investigations to observe the concentration of NO in the brain with AD and later showed that the concentration of NO is decreased through examining the concentration of transmitters related with NO in cerebrospinal fluid (CSF). Barford *et al* reported that tetrahydrobiopterin (BH4), which is a co-enzyme of NOS [188], is decreased significantly in the AD brain [189]. The reduction of BH4 might induce a diminished NOS activity that then might deteriorate neuronal function and lead to a decrease of NO production in AD [190]. Toghi *et al* reported, which agreed with Lowe *et al* [191], that L-glutamate that is released through stimulation by NO is decreased in the CSF in the AD brain [134]. Kuiper *et al* further confirmed this result and even found that the reduction of the level of glutamate is linked with the increasing age in the patients with AD [192]. The decrease of L-glutamate might therefore contribute to memory impairment in patients with AD [193]. Kuiper *et al* also reported that the nitrate content that is rapidly oxidized from NO is decreased in CSF in AD [194]. The findings suggested that the development of AD might be due to a decrease of NO synthesis [192]. Pazzo *et al* used an NO donor and inhibitor in animal models with AD and suggested that Aβ-impaired NO generation resulted from reducing NMDA receptor signal

transduction via subtracting NADPH availability to NOS [195, 196]. They and others also found that NO had a protective effect on Aβ-induced damage of the nervous system [195, 197]. In addition, it was reported that administration of NOS inhibitors did not protect against Aβ-induced neurotoxicity but that administration of NO donors did exert a neuroprotective effect [198].

On the other hand, Manh *et al* gave chronic intravenous injection of Aβ1-40 into the hippocampus in rat models. Then they found that the expression of iNOS and the production of iNO are increased, while the release of acetylcholine (Ach) and dopamine is decreased, a situation believed to be one of the primary causes of cognitive deficits in patients with AD. The rats were then treated with iNOS inhibitors. As a result, the inhibitor of iNOS restored the impairment of Ach and dopamine release and prevented memory impairment. The study indicated the toxic effect of Aβ on brain function due to NO synthesized by iNOS via dysfunction of cholinergic signaling and that, if treated with iNOS inhibitors, cholinergic dysfunction and memory performance could improve [199]. As an essential transmitter, iNO may contribute to the generation and development of AD.

Why are there so many different results about whether NO is beneficial or harmful to AD? Some studies revealed that NO is a neurotoxic factor in Aβ-induced synaptic dysfunction and cell death through stimulating iNOS, but not eNOS and nNOS [196, 200-203]. Furthermore, an increase in hippocampal iNOS and a decrease in nNOS in aged rats were observed [204]. So these effects might explain the conflicts about synaptic dysfunction due to activation of iNOS and the lack of synaptic plasticity for downregulation of NO production [205].

In conclusion, eNO and nNO, but not iNO, as transmitters, may have a neuroprotective effect against Aβ-induced impairment of LTP and ameliorate cognition in patients with AD, though additional studies are warranted.

The Effects of L-Arg on AD via Regulating Glucose Metabolism and Insulin Activity

The Relationship between Glucose Metabolism, Insulin Activity and AD

Converging evidence has confirmed that a potential association exists among metabolism of glucose, insulin activity and AD [206].

Metabolism of glucose appears to play a role in memory. Patients with AD have showed particular abnormalities of glucose homeostasis [207, 208], such as decreased glucose metabolism in the hippocampus, superior and middle temporal gyri and the cingulated gyrus [209, 210] via CMRglc or PET [211-217]. Craft *et al* examined the effects of acute glucose administration on memory in patients with AD and age-matched controls. Glucose administration temporarily improved memory function in both AD patients and controls. However, as compared with controls, it took the AD patients much longer for their glucose levels to return to baseline. The study suggested that patients with AD have less efficient glucoregulation as compared with controls and that efficient glucoregulation improves memory in patients with AD [218]. The same results were found in other studies [219-222]. Furthermore, it was investigated that acutely raising plasma or cerebral glucose levels facilitated non-contextual and contextual verbal memory, visual memory, and produced beneficial effects in a variety of learning paradigms. The same effects occurred in patients with AD who accepted acute administration of glucose [218, 223-225].

Administration of glucose with optimal doses might modulate ACh release related with cognition and learning [226]. It was also found out that administration of glucose could reverse deficits induced by cholinergic blockade [227-230] and even directly interact with other neurotransmitter systems including the gamma-aminobutyric acid (GABA) system [231]. The effects of glucose were dose-dependent with an inverted U-shaped function [226, 229]. Specifically, acute hyperglycemia can facilitate memory, whereas chronic hyperglycemia may impair memory, at least in older adults [232]. On the other hand, some investigators found that DM might be associated with an increased risk of developing AD and might affect cognitive systems differently [233-235].

Mild-to-moderate cognitive dysfunction in patients with type I and type II diabetes mellitus (DM1, DM2) may be caused by chronic hyperglycemia [236-238] or insulin

resistance syndrome [239]. Hoyer *et al* established an animal model that mimics the abnormal cerebral glucose/energy metabolism through inhibiting the neuronal insulin receptor to show that oxidative/energy metabolism, phospholipids composition of membranes, cholinergic and catecholaminergic functions, learning memory, and cognition are abnormal as seen in AD [240]. Those findings agree with other studies [241, 242]. Patients with moderate-to-severe AD have also had elevated true plasma insulin levels and decreased CSF insulin levels [243]. Studies showed that AD might be associated with reduced insulin sensitivity [244]. Other clinical studies showed that induced hyperinsulinemia while maintaining euglycemia could facilitate memory for patients with AD and normal adults [245-247]. All of the previous studies revealed that peripheral insulin abnormalities are associated with AD [248].

Raising peripheral insulin levels can improve memory when the level of plasma glucose is normal as insulin might modulate LTP through increasing the cell membrane expression of NMDA receptors [249]. After activity of NMDA receptor, neuronal Ca^{2+} influx is increased to activate α-calcium/calmodulin-dependent-kinase II (aCaMK II) and other Ca^{2+} dependent enzymes, and, finally to boost synaptic associations between neurons [250].

In summary, it is possible that abnormal glucose metabolism and impaired insulin activity contribute to cognitive decline in patients with AD. Regulating glucose metabolism and insulin activity may have positive impacts on these patients.

L-Arg might have Therapeutic Potential in AD through Regulating Glucose Metabolism and Insulin Activity

In DM, impaired production of NO results in impaired NO activity because of the uncoupling of receptor-mediated signal transduction [251-253], a deficiency of the NOS substrate L-arg [254-256], or a reduced availability of one or more cofactors essential for optimal functioning of NOS [257-259]. Excitingly, it was found that L-arg can modulate the glucose metabolism via increasing NO synthesis [260, 261] to normalize plasma glucose levels [262] and attenuate hyperglycemia [263].

Some observations of possible mechanisms about L-arg and NO to regulate metabolism of glucose and insulin activity are as follows.

First, NO normalizes metabolism of glucose via increasing glucose transport. NO donors have increased glucose transport in skeletal muscle, while inhibition of NOS activity blunted contraction-stimulated glucose transport and had no effect on insulin-stimulated glucose transport [264]. Similar results were found from a human vascular smooth muscle cell culture and adipose tissues [265, 266]. These studies showed that NO is capable of stimulating glucose transport through glucose transporter 4 translocation via insulin signaling pathway and the other mechanisms [264-266].

Second, NO increases glucose uptake in various cells. Acute infusion of NO donor resulted in greater glucose uptake, as studies have reported [267, 268]. However, NO has been implicated as an important signaling molecule in the contraction-mediated glucose uptake pathway at low concentrations, and, as an inhibitory molecule at higher concentrations [269, 270].

Third, L-arg regulates insulin release. L-arg stimulates glucose-induced insulin secretion via the NO pathway [271, 272]. It is assayed by the demonstration of expression and production of NOS in insulinoma and primary β-cells, and the insulinotropic action of NO [271]. In addition, L-arg stimulates glucose-induced insulin secretion from pancreatic islets that could occur independently of NO. The secretion of insulin by L-arg is mediated by membrane depolarization via protein kinase A- and C- activation and L-arg-induced Ca^{2+} influx [273]. It was also reported that liver cells can be engineered to produce insulin, and insulin secretion can be induced through treatment with L-arg via the production of NO [274], actions that happen when hepatic NOS are involved in the secretion of a hepatic insulin sensitizing substance that mediates peripheral insulin sensitivity [275].

Fourth, L-arg and NO enhance insulin sensitivity. Guarino *et al* confirmed from that study that insulin sensitivity is enhanced in a dose-dependent manner by co-administration of NO and glutathione (GSH) to the liver [276]. NOS protein expression that is enhanced by chronic exercise implied that NO may play a role in the improved glucose tolerance and

increased insulin sensitivity characteristic of a trained state [264]. However, some studies showed that deficiency of NO increases insulin sensitivity via modified insulin binding capacity and downregulates the expression of gene encoding resistin [277]. Finally, a study showed systemic NOS inhibition could increase human insulin sensitivity [278].

In conclusion, L-arg and NO can regulate the metabolism of glucose and insulin activity that affects AD. Further studies are needed.

The Effects of L-Arg on AD via Neurogenesis

The Relationship between Neurogenesis and AD

One of the characteristics of AD is the loss of neurons [1-4]. Recent studies provide new therapeutic strategies in the treatment of neurodegenerative diseases such as AD including the use of drugs and the transplant of tissues from the ventral mesencephalon [279-285]. An alternate approach is to target neurogenesis.

Neurogenesis in the adult brain of most mammals takes place from neural precursor cells that are derived from adult stem cells in the subgranular cell layer of the dentate gyrus of the hippocampus and in the subventricular zone of the lateral ventricle [286-289]. Precursors divide in the dentate gyrus, mature in the granular cell layer, migrate within the rostral migratory stream, and differentiate rapidly to functionally recruit the lost ones [290-294]. Recent studies have also shown that stem cells isolated from bone marrow or the umbilical cord differentiate into neural precursor cells and neural cell types under specific conditions [295-300]. They even engraft and partially correct a lesion when transplanted into Parkinson disease (PD) models [301-303]. These functional recruits occur and can be enhanced after neurogenesis [304], and are integrated both structurally and functionally into pre-existing neuronal networks [305, 306]. Such findings indicate that neurogenesis in the brain might have potential therapeutic use.

L-arg is attracting increasing attention as a regulator in neurogenesis and apoptosis. Many researchers show that L-arg is involved in different types of cell generation and apoptosis through the following major metabolic pathways [307-315].

The Effects of L-Arg on Neurogenesis through the Arginase Pathway

Sara *et al* showed that proliferation of neural stem cells (NSCs) is increased under AI deficiency in a mouse model and that derived NSCs matured and differentiated into neurons more quickly than their counterparts [316]. In addition, it was found that overexpression of AI could accelerate the extension of neurite in older dorsal root ganglial neurons [317, 318]. Extracellular administration of arginase can be antiapoptotic under oxidative stress and the other conditions that induce neuronal apoptosis [319]. Esteve *et al* also found that arginase acts as a central regulator of trophic factor-deprived motor neuronal survival [320]. These primary *in vivo* and *in vitro* studies indicate that arginase plays a role in the neural cell cycle. Du *et al* even used arginase as a therapeutic factor to treat focal brain ischemia by combining antiexcitotoxic and antiapoptotic measures rather than using either agent alone [321, 322].

The mechanisms of arginase in neurogenesis are supposed to be as follows: 1) Arginase controls cell proliferation through modulating the number of neural cells in the S-phase of the cell cycle [35]; 2) The expression of genes in cell growth is elevated to increase proliferation but not differentiation during a deficiency of arginase [35]; 3) Arginase is increased as a response of cAMP which is a crucial downstream component of the neurotrophin-induced "regeneration" pathway [47, 323]; 4) Neuron cell survival is increased and apoptosis is decreased through the administration of arginase, a phenomenon possibly due to its clearing up of excitotoxic necrosis in cortical neuronal cultures by reducing the production of NOS [82] and thereby inhibiting NO production [35]; 5) Esch *et al* demonstrated that the function of arginase to antiapoptosis depended on the depletion of arginine and the inhibition of "death proteins" synthesis [319] which is similar to the findings by Sonoki *et al* [325]; 6) Arginase exerts its function also through its products: polyamines, which play bivalent functions in neural cell growth and death [326].

Emerging evidence has proved that polyamines are involved in the development of

the CNS [327, 328]. Depletion of polyamines during nervous system development will lead to a deficiency of neuronal morphogenesis [329]. Chu *et al* showed that polyamines are able to improve axonal regeneration of neurons after injury [330, 331]. Malaterre *et al* found that neural progenitor proliferation is significantly increased in dentate gyrus and in the subventricular zone in a rodent brain when it is given putrescine. Conversely, the reduction of polyamines decreases the proliferation of an adult neural progenitor [332]. Cayre *et al* reported that the short-chain putrescine can induce neuronal precursor cells to mitogenesis and, hence, increase proliferation, while the long-chain spermidine and spermine fail to do. In contrast, spermidine and spermine can simulate neuron differentiation and neurite elongation, whereas putrescine cannot alter any morphological character of these interneurons *in vitro*. It is believed that short-chain and long-chain polyamines play specific roles during neurogenesis [333]. Putrescine enhances neuronal proliferation through regulating proto-oncogene transcription and expression, and acting on cell cyclins [334, 335]. Spermidine and spermine enhance differentiation through affecting the major cytoskeletal elements [336], and regulating casein kinase II activity, which participates in neurogenesis [337, 338].

Polyamines are involved in neuronal survival and apoptosis in concentration-dependent manner [330]. Overproduction of polyamines and the increase of their activities can induce death of fibroblasts [339, 340]. Sparapani *et al* found that high concentrations of polyamines are toxic to granule cells in culture. This toxicity is mediated through the NMDA receptor by interaction of exogenously added polyamines with endogenous glutamate released by neurons in the medium, especially spermine and spermidine [341]. In serum-containing medium, polyamines can be cytotoxic while they oxidize to aminoaldehyde and hydrogen peroxide by polyamine oxidases [342-344]. On the other hand, lower concentrations of polyamines prevent apoptotic neuronal death and toxin-and axotomy-induced cell death of sympathetic neurons in cell culture [330]. This protective function is exerted through both NMDA receptor-dependent process that enhance the activities of glutamate and NMDA at the NMDA receptor via the allosteric mechanism [345] and independent mechanisms [330]. These findings agree with those from other studies [346]. Furthermore, it was reported that only spermine promoted neuronal survival by its trophic effects through an ifenprodil-sensitive mechanism [331, 347, 348].

According to previous studies, suitable concentrations of polyamines are neuroprotective in neurodegenerative models [349, 350], such as ischemic stroke [351]. However, results are contradictory on whether using a polyamine synthesis inhibitor is also neuroprotective in stroke models [352, 353]. Rao *et al* showed that blood-brain barrier breakdown is more severe by putrescine, while breakdown is attenuated by spermine and spermidine after ischemia [353]. However, in stroke models, putrescine is increased, while there is no change of spermine and spermidine, and inhibitor of polyamines did not reduce spermine and spermidine [354]. Further studies are necessary to understand the exact roles of polyamines in such pathological conditions [353-355].

Collectively, in the metabolism of L-arg, arginase can decrease proliferation and differentiation in neurogenesis, whereas it can prevent neuron apoptosis and induce neuron survival. Polyamines, products of L-arg through the arginase pathway, have their specific functions in neurogenesis according to the length of carbon chain. Varying suitable concentrations of polyamines exist both in physiological and pathological conditions that can exert a positive impact on neuronal survival.

The Effect of L-Arg on Neurogenesis through the NOS Pathway

Growing evidence reveals that NO plays a critical role in regulating neurogenesis, neural survival, and apoptosis in CNS. It is reported that NO regulates both proliferation and differentiation of neural stem cells and neural precursor cells. Elisabetta *et al* showed that the effect of NO deprivation during the early cerebellar neurogenesis not only stimulates a brief increase in cell proliferation through reducing availability of cGMP, but also traces into adulthood in rats brain [356]. Torroglosa *et al* found that NO, as a negative regulator, decreased subventricular zone stem cell proliferation through inhibition of epidermal growth factor receptor and phosphoinositide-3-

kinase/Akt pathway, producing an antimitotic effect on neurosphere cells in adult mice [357]. Lopez *et al* also reported that NO physiologically inhibited neurogenesis in the adult mouse subventricular zone and olfactory bulb by controlling the size of the undifferentiated precursor pool and promoting neuronal differentiation [358]. Cheng *et al* demonstrated that the regulation of neurogenesis by NO occurs by its action in a positive feedback loop with brain-derived neurotrophic factor (BDNF) [359]. On the other hand, chronic administration of inhibitor of NOS enhanced neurosphere formation and growth [357], increased proliferation, and decreased the differentiation of precursors [358-360].

However, Zhang *et al* suggested that administration of NO can remarkably increase neuronal progenitor cell proliferation, differentiation, and migration in subventricular zone and the dentate gyrus of the hippocampus of the adult rodent brain [361]. Cheng *et al* also reported that NO induced apoptosis of neural progenitor cells through the p38 MAP kinase pathway [362]. Other studies showed that the apoptosis of neurons is due to oxidative injury induced by NO, which acts as a general trigger [363-365]. On the other hand, stem cell survival in nNOS knockdown animals was increased [366]. The discrepant results might be due to different isoforms of NOS involved in neurogenesis.

Sabrina *et al* found that nNOS has a primary regulatory role in the migration and survival of newly formed neuronal cells, whereas its effect upon stem cell proliferation is less pronounced [367]. In contrast, it is reported that nNOS slows down cell proliferation *in vitro* [368] and signals surviving cells to switch to terminal neuronal differentiation [359, 368]. Also, the administration of nNOS inhibitor enhances cell proliferation [369]. The mechanism behind this might be that nNOS cooperates with BDNF as a positive feedback loop to regulate neural progenitor cell proliferation and differentiation in the mammalian brain [359, 370]. However, a further study showed no difference in the changes of BDNF mRNA or protein in nNOS knockout mice. That suggested that the function of nNOS, when involved in neurogenesis, might be not only dependent on the manner of BDNF, but also another unclear pathway that indirectly switches the young neural cells from survival to differentiation [367].

Andreas *et al* showed a significant decrease of neuronal progenitor cell proliferation in the dentate gyrus in eNOS knockout mice, accompanied by a reduction in vascular endothelial growth factor (VEGF), without any changes in survival rate of newly formed cells [371]. Other studies also agreed that disruption of eNOS results in significantly decreased levels of VEGF [372, 373]. It suggests that the mechanism of selective effects of eNOS on progenitor cells proliferation might be mediated by regulating the transcription of VEGF in the hippocampus [373] to activated kinase Akt so as to downstream mechanisms and multiple pathways [371, 374, 375]. Conversely, elevating VEGF stimulates the increase of eNO through enhancing eNOS expression [146], which finally results in neurogenesis and angiogenesis that each benefits the other [141, 147]. This reveals that eNOS and VEGF act in a positive feedforward loop [371]. eNOS regulates neurogenesis through the VEGF-mediated manner, while nNOS appears to regulate neurogenesis not only by a BDNF-mediated manner. It demonstrated that nNOS and eNOS exert their effects, by indirect mechanisms, as antagonists in different phases of adult neurogenesis.

Zhu *et al* found that the expression and enzymatic activities of iNOS are elevated in the dentate gyrus after cerebral ischemia [378]. Later their further studies indicated that iNOS is crucial to accelerate neurogenesis, which is associated with enhancing cell proliferation and increasing mature granule neurons in the same area after cerebral ischemia [149]. While using the inhibitor of iNOS or antagonist of NMDA receptor, no increase of neurogenesis was observed [379-381]. It was reported that iNOS is activated quickly through activation of NMDA receptors [382, 383]. It was also reported that the reduction of nNOS and eNOS activities induce iNOS expression which produces iNO to stimulate cell proliferating factors through activated nuclear factor-β in the hippocampus [384, 385]. It also suggested that nNOS and iNOS play an opposite role in regulating neurogenesis in the ischemic hippocampus [384, 385]. However, under physiological conditions, nNO that derived from nNOS depresses iNOS expression

by inhibiting nuclear factor-NFκB activation [386].

Collectively, the metabolism of L-arg through the NOS pathway produces both positive and negative effects on neurogenesis. The authors suggest that the phenomena may be explained by the different function of three isoforms of NOS on neurogenesis. However, more research is recommended on this issue.

In summary, neurogenesis therapies involving stem cells and lineage-committed precursor cells are revolutionizing the concept of neurogenerative medicine. It is being increasingly accepted that generation and transplantation of lineage-committed precursor cells are very important steps in the process. However, the environmental and neurotrophic factors including inducible signals and transmitters around precursors and stem cells are critical to the success of therapy. In this context, we elucidate that L-arg is involved in neurogenesis through its metabolic pathways and its products. Better understanding of the metabolic procedures of L-arg would allow us to selectively choose to accelerate or attenuate some of those metabolic steps so as to contribute a valuable course to neurogenerative therapies for AD.

Conclusion

L-arg is an essential amino acid, involved in diverse physiological and pathological processes, including neurotransmission, neurogenesis and neuroplasticity, cellular redox metabolism and redox stress, inflammation, and regulation of cerebral blood flow. Increasing evidence implicates L-arg in the pathogenesis of diverse age-related diseases, including Alzheimer's disease. Understanding of the precise biochemical roles of L-arg will aid to rational development of therapeutic agents for various relevant human diseases intervention.

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