https://doi.org/10.5607/en25006
Exp Neurobiol. 2025 Apr;34(2):49-52.
pISSN 1226-2560 • eISSN 2093-8144

Review Article

Experimental Neurobiology

Astrocytic Ornithine Decarboxylase 1 in Alzheimer's Disease

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Recent research has shed light on the metabolic changes in reactive astrocytes associated with Alzheimer's disease, contributing to disease pathology. In this article, we summarize key findings related to reactive astrogliosis and how the discovery of the role of the enzyme ornithine decarboxylase 1 can set us on the path to finding more effective therapeutic strategies against neurodegenerative diseases.

Key words: Astrocyte, Alzheimer's disease, Urea cycle

Alzheimer's disease (AD) is a condition that slowly destroys memory and thinking abilities. A key feature of AD is the buildup of harmful proteins, beta-amyloid (Aβ) and tau, in the brain. These proteins damage brain cells, leading to their death. Another important change in AD involves non-neuronal brain cells called astrocytes, which become reactive and show drastic changes in their morphology and metabolism. Changes in astrocytes have been observed in the brain even before memory loss or protein accumulation appears, making these cells critical in the study of disease progression and prevention.

In a healthy brain, astrocytes help regulate neurotransmitters—chemicals that allow neurons to communicate efficiently. But in AD, astrocytes start producing too much of a neurotransmitter called γ-aminobutyric acid, or GABA, in a process that additionally produces harmful byproducts like ammonia (NH_3) and hydrogen peroxide (H_2O_2), which inhibits neuronal transmission and contributes to neuronal death, making memory problems worse.

Scientists have been studying to find a link between the accumulation of amyloid proteins and the metabolic changes that make astrocytes reactive. Recent findings by Ju et al. [1], show that astrocytes, in their attempt to clean up Aβ plaques, cause a metabolic switch in urea metabolism. The urea cycle is usually found in the liver, where it helps remove toxic ammonia from the body. Recent studies have suggested that a version of this cycle also exists in the brain. The authors find that healthy astrocytes process urea in a non-cyclic manner, with low expression of enzymes ornithine transcarbamylase (OTC) and ornithine decarboxylase (ODC1) (Fig.1, left). Without the conversion of ornithine to citrulline or putrescine, most of the metabolites entering the pathway would presumably be converted to urea and excreted as waste via the glymphatic system. They find, however, that urea metabolism switches to a cycle, with elevated expression of OTC and ODC1, and is overdriven in AD (seen by elevated brain urea levels), having both helpful and harmful effects [1] (Fig. 1, right). On one hand, the urea cycle (and upstream autophagy) helps remove toxic substances like Aβ and ammonia. On the other hand, overproduction of ornithine leads to the overexpression of enzyme ODC1 which produces putrescine, a compound that is metabolized to form harmful by-products like GABA, H_2O_2 and NH_3. The ammonia thus produced feeds back into the urea cycle, thus creating a vicious loop that adds to the toxicity created by reactive astrogliosis (See Fig. 1).

METABOLIC CHANGES IN AD ASTROCYTES: AUTOPHAGY AND THE UREA CYCLE

The researchers confirmed these findings by observing increased expression of urea cycle enzymes as well as ODC1 in astrocytes

Submitted February 26, 2025, Revised April 4, 2025,
Accepted April 7, 2025

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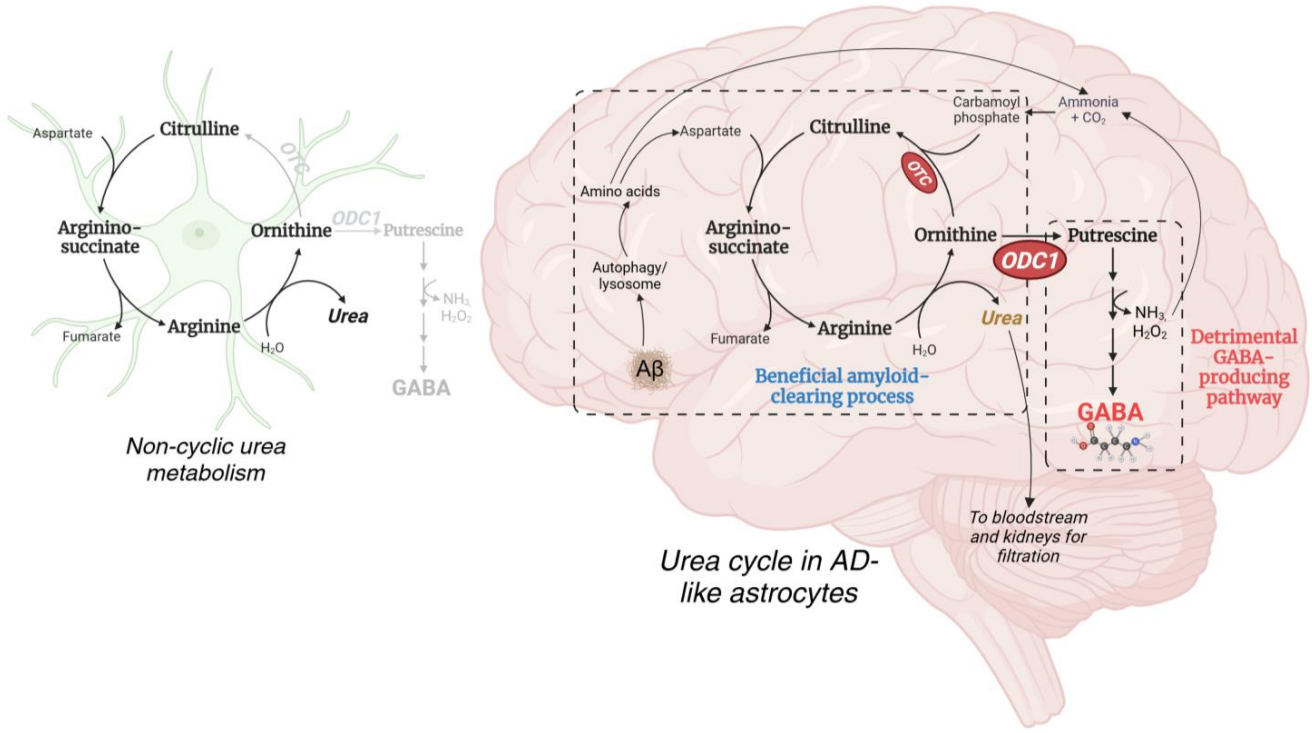

Fig. 1. Astrocytic urea metabolism in normal (left) and AD condition (right). Healthy astrocytes follow non-cyclic urea metabolism (with low expression of enzymes OTC and ODC1), while reactive astrocytes switch to the urea cycle, as seen by the expression of enzymes ODC1 and OTC. The schematic on the right shows the dichotomy of beneficial amyloid clearance and detrimental GABA and H_2O_2 production in reactive astrocytes by the urea cycle, with ODC1 as the bridge. Aβ, Amyloid beta; ODC1, Ornithine Decarboxylase 1; OTC, Ornithine Transcarbamylase; NH_3, Ammonia; GABA, γ aminobutyric acid; H_2O_2, hydrogen peroxide. Adapted from Ju et al. [1]. Created on biorender.com.

from AD patients and mouse models [1]. Elevated expression of OTC and ODC1 in human AD patients [1] indicate disease-associated expression, while increased brain urea, metabolites and expression of the upstream enzyme arginase 1 (ARG1) reflects that the pathway functions in overdrive. Interestingly, while the inhibition of ARG1 was able to reduce GABA production, it had no significant effect on H_2O_2 and Aβ plaques, making it less-than-ideal as a drug target since it hindered urea metabolism and prevented efficient clean-up of the accumulated protein [1]. Inhibition of ODC1 with a drug called DFMO (difluoromethyl ornithine) reduced the production of toxic by-products NH_3 and H_2O_2 and genetic inhibition also improved memory in AD mice. In the absence or inhibition of the enzyme, the urea cycle favored conversion of ornithine to citrulline (and glutamate) over putrescine, reducing GABA and producing urea at a faster rate [1]. Unchanged level of brain urea along with elevated expression of the urea transporter B (UT-B) upon DFMO treatment implicated efficient removal of urea from the brain by astrocytes, to be processed and excreted out of the body as urine, thereby having no adverse effect on the animal [1].

The involvement of astrocyte autophagic plasticity upstream to the urea cycle was also confirmed in a study published in late 2024 by Kim et al. [2], adding significance to these findings. Autophagy is the cellular process of engulfment, breakdown and recycling of cellular structures or components, usually in response to stress or cellular starvation. When Aβ accumulates in the brain, astrocytes induce autophagy to effectively clear it out, thereby influencing the urea cycle due to accumulation of breakdown products within the cell. The inhibition of this autophagic flux was found to exacerbate oxidative stress and reduce the production of urea cycle metabolites in the cells. The sufficiency of astrocyte autophagy was further confirmed by the astrocyte-specific overexpression of LC3B (microtubule-associated protein 1 light chain 3 beta), a protein associated with autophagosome biogenesis, which improved clearance of Aβ plaques and rescued memory [2].

A POTENTIAL NEW TREATMENT TARGET: ODC1

Astrocytic ODC1-inhibited AD mice showed fewer Aβ plaques in the hippocampus, suggesting efficient breakdown and cleanup of the accumulated proteins [1]. These findings were further emphasized, when the long-term inhibition of ODC1 in astrocytes

 https://doi.org/10.5607/en25006

led to the complete removal of Aβ accumulations from the brain [3]. Inhibiting the production of putrescine from ornithine not only reduced Aβ load but also coerced the astrocytes into a neuroprotective state, as observed by the expression of proBDNF (pro-brain derived neurogenic factor). They found that these protective astrocytes, termed as 'active' astrocytes [4], had genetic similarities with the brain environment post-exercise or environmental enrichment, both of which are known to be associated with neural regeneration [5].

ODC1 and its pharmacological inhibition has been studied in the context of cancer therapies, with largely favorable outcomes [6, 7]. Polyamine biosynthesis, an important metabolic process in rapidly dividing cells, begins with the conversion of ornithine to putrescine or spermine/spermidine by ODC1. While inhibiting ODC1 by DFMO depletes cellular putrescine levels, reducing cell proliferation and suppressing carcinogenesis, the unintended and often irreversible side effects of the compound [8] keep it from widespread use in chemoprevention [9]. Additionally, the covalent bonding between DFMO and ODC1 accelerates clearance of irreversibly bound-ODC1 and increases compensatory production of fresh ODC1 [10], altogether creating the need for better and reversible ODC1 inhibitors that can be administered long-term with minimal side effects and compensatory changes.

While it is clear that manipulation of ODC1 in astrocytes can stop the harmful effects downstream to the urea cycle while preserving its beneficial role in clearing toxic substances from the brain (Fig. 1, right), more research is needed to develop efficient therapeutics.

A POTENTIAL NEW DIAGNOSTIC BIOMARKER: ODC1

Elevated brain urea levels have been observed in Huntington's disease (HDD) [11] and Parkinson's disease (PD) [12], and changes in UT-B expression in the *glia limitans* have been observed post-TBI (traumatic brain injury) [13], suggesting that similar metabolic changes revolving around the urea cycle occur in the astrocytes of these diseases. Since HDD, PD and TBI are also known to be associated with reactive astrogliosis [14], it can, therefore, be extrapolated that ODC1 is overexpressed or turned on in these diseases, specially in diseases having accumulation of misfolded proteins (PD, HDD) or cellular damage requiring autophagic cleanup (stroke, TBI). It would be essential to study this possibility and understand the role of the urea cycle in reactive astrocytes associated with these diseases. Immunostained microscopic images of hippocampal astrocytes in the brains of healthy and AD patients reveal that ODC1 is highly overexpressed, and perhaps specifically turned on in AD, a finding that is also replicated in the AD mouse model APP/PS1 [1]. This suggests that ODC1 could be a reactive astrocyte-specific gene and can therefore, be used to check for the presence of these harmful cells. This brings forth the exciting possibility of using radio-labelled ligands of ODC1, such as ^{18}F-DFMO, as PET (positron emission tomography) tracers for the early and accurate diagnosis of astrogliosis-associated neurodegenerative diseases, which seems promising and awaits future research.

FUTURE DIRECTIONS AND CHALLENGES

Most therapeutics designed so far for the treatment of AD have targeted the accumulated proteins in the brain and have failed in clinical trials [15]. While the findings from the aforementioned studies are exciting, more research is needed in order to successfully translate them to clinical settings. Research performed by Ju et al. [1], Bhalla and Lee [3] as well as Kim et al. [2] have only been done in specific AD mouse models, which are known to represent human AD inadequately. ODC1 inhibitors approved for clinical administration are far and few, and while DFMO shows promise in animal models, it has failed in a single-subject AD case study [16] and causes side effects with long-term administration [8], imploring the need for better therapeutics. ODC1 catalyzes the rate-limiting step in polyamine synthesis, an important part of amino acid metabolism and cellular proliferation and regeneration, essential for liver function [17]. Pilot studies have found also ODC1 to play a role in reactive oxygen species-induced apoptosis in macrophages, further highlighting the important physiological functions carried out by the enzyme that need to be considered when designing therapeutic strategies [18]. Scientists are now working on creating safer, more effective drugs to block ODC1 without disrupting the urea cycle's helpful functions.

In summary, we now have new insight on how astrocytes play a dichotomous role in the pathogenesis of Alzheimer's disease, with ODC1 being the bridge between the beneficial Aβ-clearing urea cycle and detrimental GABA and H_2O_2-producing pathway. By understanding and manipulating the urea cycle and expression of ODC1 in the brain, researchers may be able to develop new therapies to combat AD more effectively.

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