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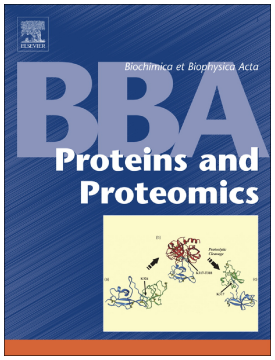

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D-serine in physiological and pathological brain aging

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Abstract

Among aging-induced impairments, those affecting cognitive functions certainly represent one the most major challenge to face to improve elderly quality of life. In last decades, our knowledge on changes in the morphology and function of neuronal networks associated with normal and pathological brain aging has rapidly progressed, initiating the development of different pharmacological and behavioural strategies to alleviate cognitive aging. In particular, experimental evidences have accumulated indicating that the communication between neurons and its plasticity gradually weakens with aging. Because of its pivotal role for brain functional plasticity, the *N*-Methyl D-Aspartate receptor subtype of glutamate receptors (NMDAr) has gathered much of the experimental interest. NMDAr activation is regulated by many mechanisms. Among is the mandatory binding of a co-agonist, such as the amino acid D-serine, in order to activate NMDAr. This mini-review presents the most recent information indicating how D-serine could contribute to mechanisms of physiological cognitive aging and also considers the divergent views relative of the role of the NMDAr co-agonist in Alzheimer's disease.

Keywords: synaptic plasticity, NMDA receptors, serine racemase, Alzheimer's disease, glutamate, L-serine

1. Introduction

Beyond increasing life expectancy, improving health status of elderly is now one of the most current important challenge to face in the field of research on ''aging processes''. Aging is a natural biological process that affects the entire body. Notably, while affecting the brain, cognitive decline and especially memory processes alterations, would play a pivotal role in the poor quality of life of elders.

Although initially associated with neuronal loss, underpinning mechanisms of brain aging still remain debated despite an extensive literature [1-5]. This may be related in part to limits of the initial stereological methods used to estimate the neuronal density [6-8]. To date, the theory that prevails does not consider the decrease in cells number as a hallmark of physiological aging, but rather to its pathological aspect such as Alzheimer disease (AD) affording neuronal and synaptic losses [3-5, 9-11].

Essential relay in the formation of many types of memory traces, the hippocampal formation has been particularly studied, both in humans and animals [12-15]. Hence, in rodents [16, 17], a decreased ability to consolidate long-term memory has been linked to a weaker capacity to express long-term potentiation (LTP) of synaptic transmission (reviewed in [18]). Besides, a rapid decay of hippocampal LTP was correlated to poor spatial memory performances in aging rats, which probably contributes to the increased propensity to forget spatial information [19]. Overall, age-induced decrease in synaptic plasticity efficiency would impaired capacity to encode and/or consolidate new memories and would be in part responsible for loss of pre-existing ones [20-22]. These synaptic functional alterations and the subsequent cognitive deficits have been linked in part to a progressive deregulation of the activation of NMDA receptors (NMDAr). NMDAr is a subtype of glutamate receptors generally views as critical to drive synaptic plasticity in many brain areas [23-26]. In addition to glutamate, NMDAr activation requires the binding of a co-agonist at its specific site. Initially attributed to glycine [27-29], subsequent studies showed that D-serine could also play this role. Indeed, both the specific degradation of the amino acid D-serine by the enzyme D-amino acid oxidase (DAAO) [30] and the genetic deletion of its synthesizing enzyme serine

racemase (SR) [31, 32], significantly altered NMDAr activation. These results therefore led to consider D-serine as the main endogenous co-agonist of synaptic NMDAr and further experiments confirmed the pivotal role of this amino acid in the regulation of functional plasticity at many synapses throughout the brain (reviewed in [33]).

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2. D-serine in physiological aging

Alterations of functional plasticity associated with cognitive impairments observed across aging naturally raised the question for a role of D-serine. Thereafter, it was observed that a supplementation with the amino acid was able to prevent age-induced deregulation of NMDAr activation and to restore hippocampal synaptic plasticity [34-37]. Beyond the decrease in NMDAr density (or its subunits) initially evoked [38-41], these promising results rather argue for a pivotal role of D-serine in functional mechanisms underlying cognitive aging [42, 43].

The beneficial effect of a D-serine supplementation could reflect a significant decrease in D-serine levels with age, as supported in rodent hippocampal assays [34-36]. Interestingly, this decrease is also found in human plasma levels [44]. Another explanation could have been a decrease in the degree of NMDAr saturation, but autoradiographic studies performed in aged rodents did not reveal changes in the specific affinity of the co-agonist binding site [34, 35, 45]. Besides, other results from preclinical investigations performed in rodents indicate that the decrease in D-serine levels could rely on a weaker SR expression both at protein and messenger RNA levels [34-36], though whether the activity of the D-serine synthesizing enzyme is altered at the same time remains to be determined. On the other hand, the expression of the catabolizing enzyme DAAO is not affected in aged animals, indicating that an acceleration of the degradation of the amino acid does not contribute to the age-related decrease in D-serine levels [34-36]. The synaptic availability of D-serine is also dependent on the activity of the Asc-1 subtype of neutral amino acid transporters, which supports the release of D-serine from neurons [46, 47]. A recent investigation indicates that Asc-1 activity remained unchanged in the aging hippocampus [48]. Considering that mechanisms underlying the degradation and release of D-serine are not altered in physiological aging, alterations in synthesis therefore appears as the critical mechanism underlying the age-related decrease of the NMDAr co-agonist availability [42, 43].

The decrease in SR expression and D-serine production possibly results from the development of the oxidative stress (OS) that normally occurs with aging [49-52]. Indeed, both deficits do not occur in the LOU/C rat [36], a model of successful aging characterized by a high degree of resistance to OS [53-56]. They are also prevented in aged animals receiving a long-term treatment with the reducing compound N-acetyl-cysteine in which the extent of OS is minimized [57]. An increased oxidation of sulfydryl groups of SR [58] and/or changes in its dimer active conformation [59] may be viewed as possible mechanisms underlying the age-

related SR deregulation by OS. Interestingly, aged LOU/C rats show not only intact synaptic plasticity and NMDAr activation but also preserved memory abilities [55, 56, 60]. Compelling all these available functional and behavioural data therefore indicates that a preservation of SR activity and a robust synaptic availability of D-serine in cerebral tissues is essential to maintain potent cognitive capacities in physiological aging (Figure 1). It is interesting to note that the impaired learning of olfactory conditioning in aged drosophila, which also display decreased D-serine levels, was reversed by feeding flies with the amino acid [61]. Nevertheless, a supplementation with D-serine to prevent memory deficits in aged mammals has not been considered yet although treatment with the related agonist D-cycloserine is clearly beneficial in aged rodents [62, 63]. This is presumably because long-term treatment with D-serine induced serious side effects, nephro- and hepato-toxicity notably [64, 65].

3. D-serine in Alzheimer's disease

Although our knowledge on pathophysiological mechanisms underlying the onset and development of Alzheimer's disease (AD) has increased exponentially these last decades, its aetiology is far from being fully clarified. Indeed, AD is complex and multifactorial, with a notable overlap between familial and sporadic forms. Its symptomatology has been associated with a convoluted and multiple mechanisms, including an increase in the production of the β-amyloid (Aβ) peptide that accumulates intracellularly while also aggregates in extracellular deposits, and enhanced intraneuronal neurofibrils with hyperphosphorylated TAU protein. These typical features are accompanied with gliosis and synaptotoxicity that finally results in neuronal loss and brain atrophy (see [66] for a review).

The NMDAr represents one of the most predominant extracellular targets for AD-related pathology. Indeed, even though still matter of debates, impairments of NMDAr are viewed as core pathophysiological mechanisms of the disease [67-69]. Whereas synaptic glutamate loss of availability is known to contribute to pathology [70, 71], changes in D-serine levels and putative underlying processes remain so far subject of controversial views.

The first link between D-serine and AD came from biochemical investigations. Indeed, either cerebrospinal fluid (CSF) or plasma changes in amino acid levels were observed in AD patients [72-80]. Unfortunately, divergent results appear from one study to another, regarding the magnitude but also the direction of these changes (Table 1). One possibility to account for

the discrepancies could be found on the Braak stage of the patients sampled since D-serine levels are thought to progressively increase in the CSF across the progression of the pathology [78]. Further, increased expression of the D-serine synthetizing enzyme was found in the hippocampus of Braak stage III-IV AD patients [81]. However, a significant rise of the co-agonist in the pathophysiology of the disease has been questioned by a subsequent analysis but the Braak stage in this study was not clearly defined [72]. Finally, it's worth mentioning that an increase level of extracellular transcript of the phosphoglycerate dehydrogenase (PHGDH) was recently reported in subjects at presymptomatic stage, i.e. before being diagnosed AD [82]. PHGDH catalyzes serine biosynthesis in the brain from glucose[83]. Therefore, the elevation of its extracellular RNA may argue for an increase of D-serine brain level during presymptomatic stage of the disease.

Similarly, this issue does not make consensus in the field of preclinical investigations ([78, 84-86], see Table 1). In fact, an increase of D-serine levels in hippocampal tissues has been observed in several animal models of AD, including those with intracerebroventricular injections of soluble oligomers of the Aβ peptide (Aβo) and genetic strains bearing several mutations associated with familiar forms of AD [78]. Thus, preliminary results in the 5xFAD mouse model of AD displaying high and chronic elevation of Aβo charge show a limited but significant increase in D-serine levels (Ploux et al, abstract IDAR 2019). It has been previously demonstrated *in-vitro* that Aβo could promote transcriptional expression of SR and stimulate D-serine release from both activated microglial cells [87, 88] and neurons [70]. More recently, induction of SR expression has also been found *in vitro* in reactive neurotoxic astrocytes [89] and *in-vivo* in the TgF344 rat model of AD [81]. Quite interestingly, SR knockout mice display significant reduced brain lesion after acute injections of Aβo [90]. Finally, our preliminary results indicate that the impairment of hippocampal synaptic plasticity and memory deficits associated with the increased D-serine levels in 5xFAD mice are rescued by a concomitant deletion of the SR gene. Altogether, this set of results supports the view that D-serine is required for the induction and development of the Aβo-dependent pathophysiology.

However, this view is not so straightforward (Figure 2). Indeed, observations from two transgenic mice models have extended the debate into the preclinical field on how D-serine contributes to AD. In fact, a decreased synthesis of L-serine from glucose though PHGDH astrocytic enzyme has recently been reported in 3xTg-AD mice [84]. Astrocytic L-serine was proposed to regulate NMDAR activity to sustain D-serine production by neurons [91] that

would thus explain the altered synaptic plasticity observed in AD. The deficits of functional plasticity in the hippocampus and memory impairments in these 3xTg-AD mice [84] are rescued by long-term treatments with either D- or L-serine, confirming the view of severe metabolic dysfunction as a leading hallmark and cause of AD as previously proposed (see [92]).

Besides, a weaker amount of the NMDAr co-agonist was observed in Amyloid Precursor Protein (APP) knock out mice [93]. This suggests that in addition to changes induced by increased synthesis of soluble Aβo, the native protein is capable by itself to regulate D-serine homeostasis.

The question of the potential modification of D-serine levels in AD and its opposite directions found in the literature, points out several important aspects, notably due to predominant role of D-serine as a NMDAr co-agonist, that remain to be solved. Several explanations could account for the controversial results resumed above. First, as recently emphasized [94], the quantification of D-serine levels must comply with strict procedures allowing a precise and specific detection of the amino acid. However, all studies aimed at quantifying D-serine did not fulfil all the validation criteria. Second, as discussed by Le Douce and colleagues [84]), results may differ from one animal model to another since each of them reproduces only partially and differently the mechanisms and severity of AD-associated pathophysiology. As for examples, the intraneuronal Aβ rates may be very different among the animal models of amyloidogenesis. Also, levels of soluble Aβo are not defined in the study of Le Douce [84] which may be too low to impact SR activity. On the other hand, the glycemia and carbohydrate status of the 5xFAD mice used in the study of Ploux et al has not yet been considered, thus questioning putative changes in L-serine availability. Advantages and limits of modelling the disease in animals has been largely considered in the literature but our review, even by focussing on the specific role of D-serine in AD, indicates that this question still remains an important and open issue [95].

3. Conclusion

Together, the results of clinical and preclinical studies show an undeniable variation in D-serine levels in both physiological and pathological aging. Regarding the first aspect, studies agree on a decrease in the availability of the amino acid that would directly impact functional synaptic plasticity and memory capacities. These data are particularly stimulating to initiate the search of future pharmacological treatments to compensate for the loss of D-serine. In

contrast, a therapeutic perspective regarding the pathological aspect of aging still remains utopic since the view of how the amino acid behaves in both humans and animal models of AD does not make consensus. Nevertheless, one may speculate that the opposite decrease or increase in D-serine levels reported along AD-related studies could be speculated as reflecting the slow development of the disease and particularly of its amyloid progression. In conditions of low Aβo production, the alteration of glucose intake and consequently the reduced production of the precursor L-serine could be considered as a critical mechanism that decreases D-serine levels in the early stages of the disease. Then, as the Aβo production elevates, this mechanism could be overpassed by the direct stimulation of SR activity, thus enhancing D-serine levels. This interesting schema has now to be precisely evaluated and represents an essential milestone since it means that the best effective therapeutic strategy of delivery of the amino acid should closely depend on the stage of the disease.

A further point remains also to be considered for the evaluation of D-serine in AD. As recently demonstrated, epigenetic mechanisms play a key role in the regulation of cerebral D-serine levels [96]. Therefore, the evaluation of the impact of epigenetics in the expression of D-serine degradation (DAAO) and synthesis (SR) enzyme genes should represent a major issue in AD.

On the other hand, this review indicates that there is still clearly a crucial need of animal models really mimicking the slow progression and the changes in Aβ and Tau protein levels of human AD. Hopefully, a new generation of models such as those currently developed with viral-mediated gene transfer [97, 98] will certainly allow for more consistent results and clearer understanding of the involvement of D-serine in the pathophysiology of AD.

Figure 1: Schematic representation of changes in D-serine availability at CA3/CA1 hippocampal synapses during physiological aging.

Once formed from glucose in astrocytes, the precursor L-serine shuttles to the neuronal compartment to be converted into D-serine by serine racemase (SR). After being released in the synaptic cleft, D-serine binds to NMDAr, together with glutamate, allowing activation of the receptor. During the aging processes, the progressive installation of the oxidative stress decreases the expression or the dimerization of SR, thus reducing D-serine synthesis. Consequently, NMDAr activation is altered that impairs the expression of functional plasticity such as long-term potentiation in neuronal networks and, ultimately of the memory encoding.

Figure 2: Schematic representation of changes in D-serine homeostasis at CA3/CA1 hippocampal synapses during the progressive installation of amyloid-related pathophysiology of AD.

At early stages of the disease with low levels of soluble Aβ oligomers (left), glucose catabolism is impacted that decreases the synthesis of the precursor L-serine, thus reducing D-serine levels. This leads to weaker NMDAr activation, impaired functional plasticity in neuronal networks and ultimately deficits of memory processes.

As levels of soluble Aβo increase (right), astrocytes become reactive and start to express SR and release high amount of D-serine. Together with the increase in synaptic availability of glutamate, the elevation of D-serine drives NMDAr over-activation resulting in excitotoxicity, neurodegeneration and profound memory deficits.

Credit author statement

EP, TF and JMB have contributed to the elaboration and writing of the review. EP has built the Table and figures.

Declaration of interests

X The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1: Comparison of the different clinical and preclinical studies aimed at measuring D-serine contents in brain tissues, blood or cerebrospinal fluid (CSF). AD: Alzheimer's disease, MCI: Mild cognitive impairment, MMSE: mini-mental state examination, HPC: hippocampus, PCF: Prefrontal cortex

	Ref n°	Subjects	AD MMSE	Sample	Cerebral region	D-serine level
	79	AD		Tissues	PFC	=
	75	AD		Tissues	PCF, parietal cortex	=

	73	AD		Tissues	Temporal cortex	=
	78	AD	12.7 (+/-6.2)	Tissues	HPC and parietal cortex	↗
		MCI, mild, moderate to severe AD		CSF		↗
	80	AD		CSF		↗
	72	AD	22.1 (+/-3.3)	CSF		=
	74	AD	18.7 (+/- 5.00)	Serum		↘
	76	Amnestic MCI, mild AD, moderate AD and severe AD		Serum		↗
	77	MCI, mild, moderate to severe AD	23.2, 18.2, 10.4, 28.1	Peripheral blood		↗
PRECLINICAL DATA	**Ref n°**	**Model**	**Age**	**Sample**	**Cerebral region**	**D-serine level**
	85	Wistar rats with Aβ injections		Tissues	Olfactory bulb, cerebellum	=
					HPC, cerebral cortex	↘
	78	APPSwe/PS1ΔE9 mice	14-16 months	Tissues	HPC	↗
		C57Bl/6 mice with Aβo injections	3 months	Tissues	HPC	↗
	84	3xTg-AD	6 months	Tissues	HPC	↘
	86	Wistar rats with Aβ injections		Plasma		↘

Highlights:

- D-serine levels decrease in physiological aging
- In Alzheimer's disease, changes in D-serine levels remain unclear
- The direction of changes may depend on the stage of the disease

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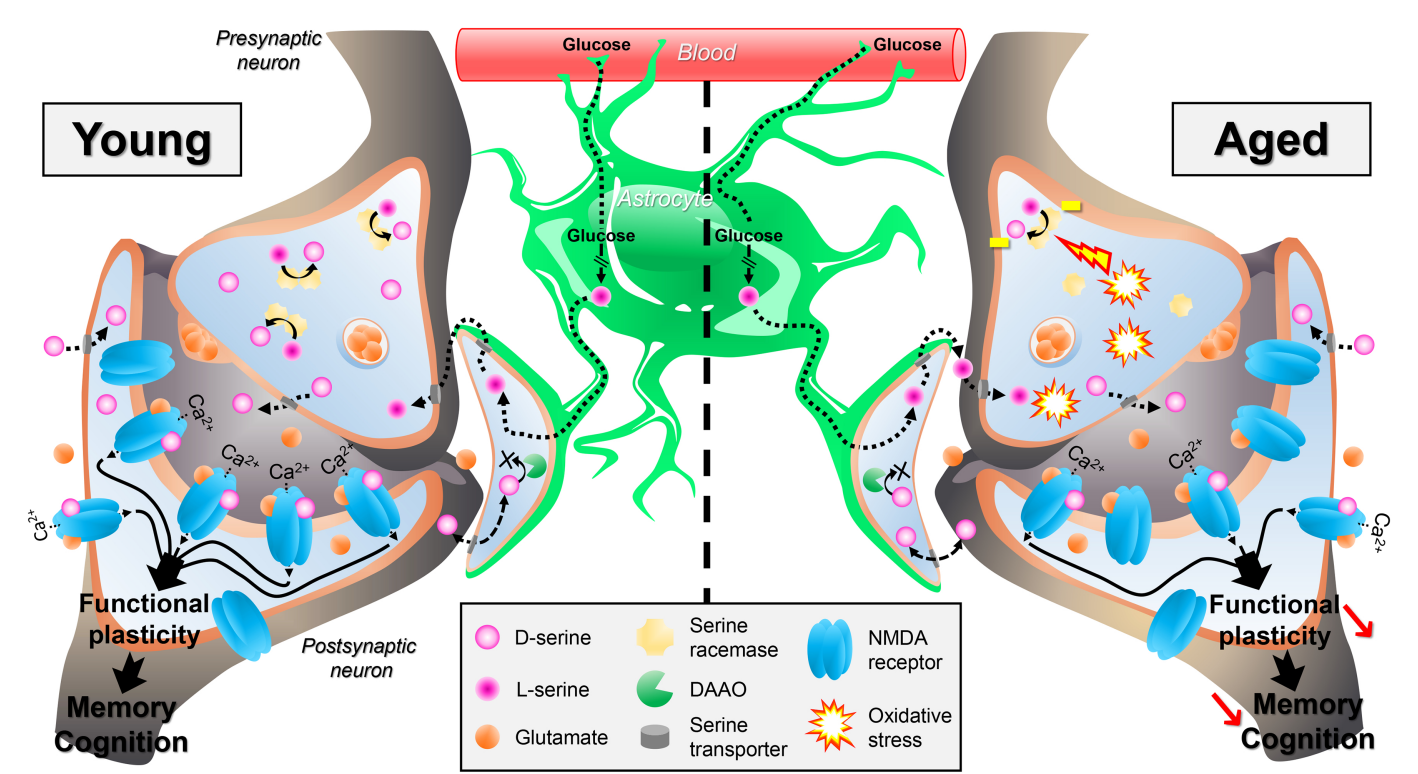
Presynaptic neuron
Young
Glucose
Blood
Glucose
Astrocyte
Glucose
Glucose
Aged
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Functional plasticity
Memory Cognition
Postsynaptic neuron
D-serine
L-serine
Glutamate
Serine racemase
DAAO
Serine transporter
NMDA receptor
Oxidative stress
Functional plasticity
Memory Cognition

Figure 1

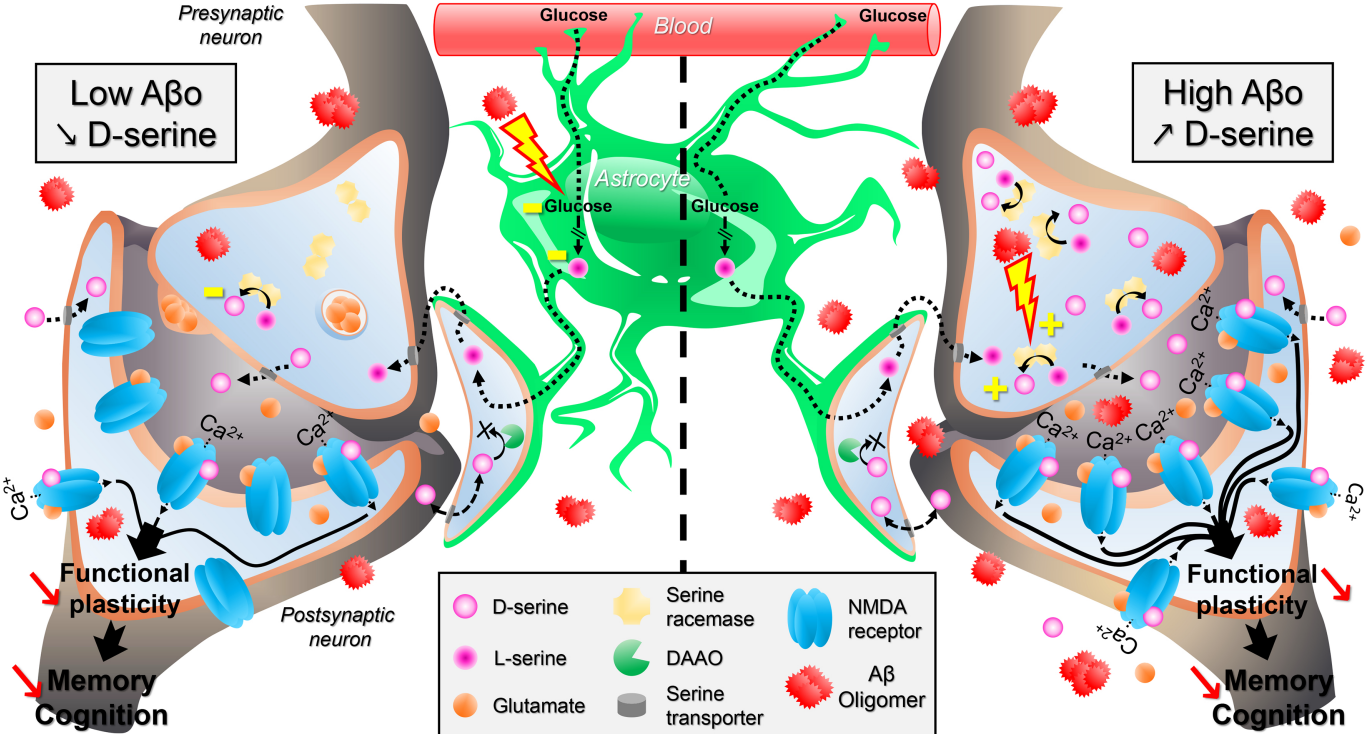
Presynaptic neuron
Glucose
Blood
Glucose
Low Aβo
↘ D-serine
Astrocyte
Glucose
Glucose
High Aβo
↗ D-serine
Ca2+
Functional plasticity
Memory Cognition
Postsynaptic neuron
D-serine
L-serine
Glutamate
Serine racemase
DAAO
Serine transporter
NMDA receptor
Aβ Oligomer
Functional plasticity
Memory Cognition

Figure 2