Alterations of astrocytic glutamate regulation in Alzheimer Disease

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Introduction

Alzheimer disease (AD) is considered the most common cause of dementia, with a prevalence of 80% in elderly.

It is an aged-related disorder characterized by a progressive neurodegeneration (especially in the hippocampus and neocortex) that correlates with memory and learning impairment.

These typical features of the disease have been related with deposition of senile plaques (accumulation of Aβ peptide) and intracellular neurofibrillary tangles (hyperphosphorylated tau protein).

Moreover, glutamate homeostasis is also altered in AD brains , leading to increased levels of extracellular glutamate. This seems to be gaining relevance in the disease development and progression.

Glutamate levels are mainly regulated by astrocytes, which actively participate in the synapse events. Thus, astrocytes role is of great importance when targeting AD pathogenesis.

Objectives

- Describing the physiological cycle of glutamate.
- Reviewing the current knowledge of dysregulations on glutamate clearance and release related to Alzheimer disease progression.
- Explaining possible causes of such alterations and their consequences.

Methodology

Scientific literature search on Pubmed database: paper and reviews were selected by relevance on journal and publication date, as well as relevant articles cited in other publications.

Official websites of Alzheimer's disease organizations and books related to neuroglia and glutamate were also consulted.

Glutamatergic system in Alzheimer disease

Glutamate cycle under physiological

Under physiological conditions, glutamate concentration within the synaptic cleft remains low. Therefore, the interplay between glutamate release and clearance is essential to tightly regulate the extracellular levels of the neurotransmitter and thereby preserve synapsis transmission (Figure 1).

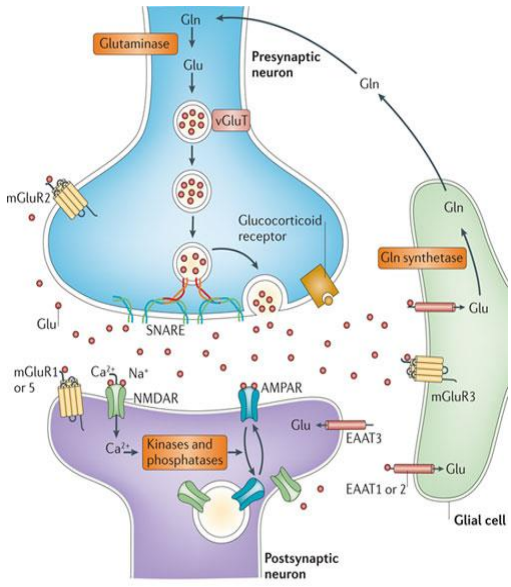


Figure 1. Glutamate physiological cycle: glutamate (Glu) is synthesized from glutamine (Gln) and then stored into synaptic vesicles. After neuronal excitation, glutamate is released into the synaptic cleft and binds to glutamate receptors (NMDAR, AMPAR, mGluR1-5). The neurotransmitter is rapidly cleared by glutamate transporters (EAAT) mainly present in glial cells. Once inside glial cells, glutamate is converted to glutamine, which is recycled back to the presynaptic neuron. [From: Nat. Rev. Neurosci. 13, 22-37 (2012)]

Astrocytes are essential to ensure that glutamate concentration is kept low and they actively participate in the synapse. In fact, astrocytes have glutamate receptors, so when the neurotransmitter is released to the synaptic cleft they can sense it and rapidly activate glutamate transporters (EAATs). These transporters are primarily responsible for glutamate uptake and are mainly present on astrocytes plasmatic membrane.

Glutamate cycle under pathological conditions

Glutamatergic system has proven to be profoundly dysregulated in AD. This results in elevated glutamate concentrations within the extracellular space, leading to a variety of consequences characteristic of the pathogenesis:

Several studies support that such alterations may be due to the observed decrease in EAATs function and protein levels. Among glutamate transporters, EAAT2/GLT-1 has been described to be the most affected in AD brains, since it is the main transporter expressed in the hippocampal region.

Moreover, under pathological conditions astrocytes can further contribute to elevate glutamate levels by releasing the neurotransmitter by themselves. This has been demonstrated to be in response of pro-inflammatory factors, oxidative stress…

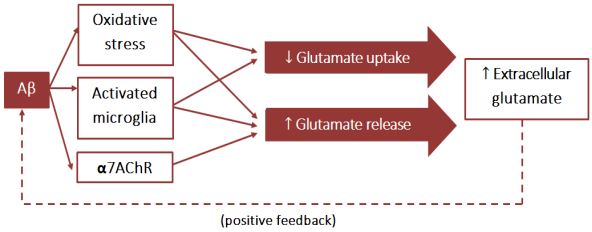
Consequences of increased glutamate levels

Elevated concentration of glutamate results in the overstimulation of its receptors, especially NMDARs. Consequently, synaptic loss and excitotoxicity are enhanced. It has been proposed that depending on NMDAR subunit, different pathways can be triggered. Indeed, high glutamate consequences seem to be regulated by different subunits [3]:

- Glu2B ➔ Excitotoxicity (tau-dependent pathway)
- Glu2A ➔ Synaptic loss (caspase signaling tau-independent pathway)

Possible causes of glutamate homeostasis disruption

The underlying causes of glutamate dysregulation are still not fully understood. However, several studies have related it with Aβ [4,5]:



Conclusions

- Glutamate homeostasis is profoundly impaired in AD and this has been related with neurodegeneration, cognitive decline, and neuroinflammation.
- It is not clear if such alterations are consequence of the disease or could be a cause.
- However, what seems to be more evident is that increasing glutamate levels contribute to AD progression.
- Moreover, focusing on glutamate transporters could be promising as a therapy.
- Therefore, it would be interesting to conduct further studies in order to better understand the mechanisms and consequences involved in their dysregulation.

Selected references

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