D J Med Sci 2020;6(2):87-91
doi: 10.5606/fng.btd.2020.25027

Review

Astrocytes and memory

Oğuzhan Kütük

Psychologist, Istanbul, Turkey

ABSTRACT

Although their presence in the brain has been discovered years ago, astrocytes have been overshadowed by neurons due to lack of research. However, thanks to studies conducted in the last 20 years, it has become clear that astrocytes play a role in many functions of the brain such as memory and learning. In addition, recent findings have shown that astrocytes are associated with learning, memory impairments, and psychiatric disorders. These studies may provide new insight into certain issues left unsolved by neurons.

Keywords: Astrocytes, glial cells, gliotransmitters, memory.

GLIAL CELLS

There are two types of nerve cells in the brain: neurons and glia. In the mid-19th century, Rudolf Virchow, a German anatomist, first described this new cell type and named them glia (glue), believing these cells acted as a sort of adhesive for the nervous system.[1] Glial cells are necessary for the development, function, and transmission of the nervous system. There are three main types of glial cells in the central nervous system (CNS): astrocytes, microglia, and oligodendrocytes. Neurons are associated with glia for physical support, nutrient supply, and clearing of extracellular molecules, as well as for enhancing and modulating signal transduction.[2] In fact, every neuron is protected by some type of glial cell.[3] At the same time, glial cells, like neurons, synthesize and release a large number of molecules. These molecules play a significant role in controlling the microarchitecture, neuronal structure and metabolism, as well as contributing to the regulation of the electrical activity of neurons. These molecules, which are synthesized and released by glial cells, are referred to as "gliotransmitters".[4-6]

THE ROLE OF ASTROCYTES IN THE BRAIN

Astrocytes are the most abundant of the glial cells and are in continuous association with most cell types in the CNS.[7]

Astrocytes have the ability to receive signals from neurons through membrane receptors and convert the received information to calcium (Ca^{2+}) excitability. The ability of astrocytes to release extracellular signaling molecules regulated by this Ca^{2+} excitability indicates that they play a very active role in the CNS. This concept of regulated transmitter release from astrocytes to neurons is commonly known as gliotransmission.[8,9] The most abundant gliotransmitters are glutamate, D-serine, and adenosine triphosphate (ATP).[7,8,10]

Received: January 28, 2020 ***Accepted:*** March 05, 2020 **Published online:** August 25, 2020

Correspondence: Oguzhan Kütük. İstanbul, Türkiye.
Tel: +90 507 - 809 22 67 e-mail: kutukoguzhan96@gmail.com

Cite this article as:
Kütük O. Astrocytes and memory. D J Med Sci 2020;6(2):87-91.

Astrocytes are especially important in the homeostasis of neurotransmitters in the brain. They contribute to the removal of many neurotransmitters from the synaptic cleft, their metabolism (glucose and lactate), and the reuptake of the two most common neurotransmitters in the brain (glutamate and gamma-aminobutyric acid [GABA]). They also play an especially significant role in preventing the accumulation and toxicity of glutamate, an important excitatory neurotransmitter, in the brain. While 20% of glutamate that is released during synaptic transport is retaken by neurons, the remaining 80% is retaken by perisynaptic astrocytes.[11-13] Removal of glutamate from the extracellular site is vital for protection against excitotoxicity, as well as initiating the glutamate-glutamine cycle, an essential cycle for re-synthesis in neurons.[4,11] Astrocytes, which are steadfast helpers of neurons in carrying out several functions in the brain, sometimes directly or indirectly contribute to learning and memory functions.[14]

THE ROLE OF GLIOTRANSMITTERS IN MEMORY

The association of astrocytes with memory is mostly through secreted gliotransmitters. One of these gliotransmitters is GABA, the main inhibitory transmitter of the brain. Astrocytes provide reuptake of GABA from synapses, without which the establishment of synaptic communication in neurons would be impossible.[15] Inadequate or excessive GABA secretion may reduce synaptic plasticity and cause memory impairment in domains including spatial memory, working memory, and fear-related memory.[16-19] Another significant gliotransmitter is glutamate, known as the major excitatory molecule of the brain. Likewise, synaptic communication cannot be established without glutamate reuptake. Glutamate is released by both astrocytes and neurons and taken up by astrocytes from the synaptic cleft and returned to perisynaptic neurons for reuse.[20] Glutamate plays a crucial role not only in synaptic transmission but also in synaptic plasticity through the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors. Glutamate has been shown to strengthen memory,[21] and has also been associated with cognitive deficits and psychiatric disorders - especially schizophrenia and Alzheimer's.[22-24] D-serine is another molecule released by astrocytes[25-27] and binds to NMDA receptors.[28] D-serine is involved in most long-term memory processes including NMDA-receptor-dependent synaptic plasticity, regulation of long-term potentiation (LTP), and hippocampal neurogenesis.[26,29,30] Studies have also demonstrated that D-serine is involved in spatial memory formation and is associated with age-related memory loss.[31,32] Recent studies have indicated that D-serine can also be released by neurons and regulate the formation of synaptic plasticity.[33] Adenosine triphosphate, another molecule released by astrocytes, is released in response to glutamate and plays a role in the formation of neural stem cells in the hippocampus.[34,35] Glutamate is taken up by astrocytes and converted by glutamine synthetase to glutamine, another important molecule of the nervous system, which is retaken by neurons to carry out its functions. The relationship between glutamine and memory was revealed in an experimental study on mice. The study found that there was a decrease in glutamine synthetase in astrocytes in the prefrontal cortex of Alzheimer-induced mice.[23]

OTHER ASTROCYTIC FUNCTIONS THAT DIRECTLY AFFECT MEMORY

As mentioned before, the relationship between molecules and memory is more indirect. However, the relationship of some substances released by astrocytes is more directly linked to memory.[36] One of these substances released by astrocytes is lactate. Neurons require glucose/lactate to carry out their functions. In one study, lactate released from astrocytes in the hippocampus was shown to play an important role in emotional memory formation in rats and learning in chicks.[37,38] In addition, these studies reported that the release of lactate from astrocytes was required for long-term memory formation (but not required for short-term memory formation) and that lactate injection to the intrahippocampal region enhanced memory.[37,38] Orally administered glucose (glucose can be converted to lactate) was found to increase cognitive functions while enhancing memory in humans and rats, and

improve verbal memory in healthy young and old people.[39-42] Another molecule associated with memory and learning is K^+. One study demonstrated that removal of K^+ from the synaptic cleft contributed to short-term plasticity formation.[43]

More important evidence of the role of astrocytes in memory was found in another experimental study on rats. In the experiment, it was found that the number of astrocytes in the CA3 region of rats increased during the Morris water-maze test (used in learning and memory experiments.[44] In a recent *in-vivo* study by Stehberg et al.,[45] gliotransmitter release of astroglial connexin 43-hemichannels in the basolateral amygdala region of rats was blocked during memory consolidation (after presenting stimuli to be remember later); 24 hours later, amnesia was observed in the rats. After the effects of amnesia, the rats were injected a cocktail consisting of gliotransmitters such as glutamate, D-serine, glutamine, ATP, and glycine, and learning capacity was recovered.

Another recently published study, Pinto-Duarte et al.[46] studied genetically engineered mice that were lacking a receptor called type 2 inositol 1,4,5-trisphosphate (IP_3R2) to understand the relationship between astrocytes and long-term memory. Astrocytes rely on these receptors to release calcium for communication.[47,48] Mice lacking Ip_3R2 receptor ($Ip_3R2^{-/-}$) were tested 24-48 hours after learning processes, and the results were similar compared to the performance of normal mice. However, when researchers retested the mice 2-4 weeks later, mice lacking the Ip_3R2 receptor performed much worse than normal mice, while normal mice showed better performance compared to their first test. This indicates that mice lacking Ip_3R2 receptors significantly lost their memory consolidation abilities.[46] The increasing understanding of the relationship between astrocytes and memory can contribute to the future development of drugs to manipulate memory consolidation and treat memory-related disorders.[5,46]

Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author received no financial support for the research and/or authorship of this article.

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