Astroglia in Memory Formation

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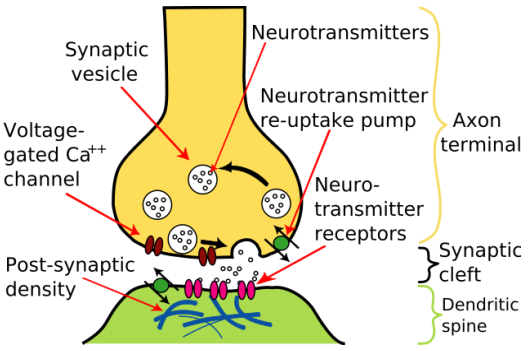
Introduction

What Is Memory?

Memory is the brain's capability to process and store information, as well as retrieve it when necessary. By being able to retain information over time, we are given the possibility to use our memory to influence our actions and decisions. There are different types of memory, such as sensory memory, working memory, short-term memory, and long-term memory. Structural plasticity, functional plasticity, and long-term potentiation (LTP) are all factors that mediate memory formation. In its regulation is where astroglia play an integral role as studies show that the involvement of astroglia is larger and more important than formerly thought.

How Are Memories Formed?

Long-term memory is divided into explicit and implicit memories. Explicit memories are ones that you can consciously recall, such as remembering what you learned in a physiology lecture. On the other hand, implicit memories, which tend to be more important, are automatic and unconscious, such as walking to a nearby store or typing on your computer. Short-term memory, also known as working memory, deals with your brain's ability to remember a small amount of information for a short period of time, such as a quick OTP bank code or a number being recited to you. (*Mendis, 2018*).



It is crucial to understand how these types of memories are formed and stored within our brain. There are different groups of neurons responsible for the reactivation of memory via their synaptic plasticity. This means that the constant changes in the synapses, the connections between brain cells, can be made stronger or weaker depending on how often they get activated. The connections that are activated more often get stronger and those that are not get weaker. Long-lasting connections in the synaptic cleft between two neuron cells leads to long-term potentiation, where our memories become stored in certain parts of our brain. The hippocampus, neocortex, and amygdala store our explicit memories, whereas our implicit memories rely on the basal ganglia and the cerebellum. Our prefrontal cortex works heavily on supporting our short-term memory. (*Mendis, 2018*)

The Brain in Memory Formation

Hippocampus

The hippocampus is located in the brain's temporal lobe, and it is where episodic memories are formed and stored for later use. Although it is crucial for setting initial memories, it is not dependent upon permanent memory storage or motor movements. It has three specific functional areas that each have an integral part in the formation of memories. These are the CA1, CA3, and dentate gyrus. Various receptors found in different areas of the hippocampus have been shown to play roles in memory formation through long term potentiation.

Neocortex

The neocortex is the largest part of the cerebral cortex that is involved in high functions such as sensory perception or generating motor command. Certain information from memories can be transferred from the hippocampus and used as general knowledge in the neocortex over time.

Amygdala

The amygdala is found in the brain's temporal lobe, and it is responsible for attaching emotional importance to certain memories. This helps with the reactivation of memories because memories with a strong emotional attachment are harder to forget. This solidifies the relationship between the amygdala, hippocampus, and neocortex, as they are all crucial in stabilizing memories and retaining them over time. The amygdala also plays a key role in creating memories associated with the emotion of fear. It is actually the main factor of post-traumatic stress disorder (PTSD), as it is able to store memories associated with emotion (*Mendis, 2018*).

Basal Ganglia and Cerebellum

Both basal ganglia and the cerebellum play a key role in implicit memory, which involves a wide range of motor movements and the formation of habits. The basal ganglia are key in co-ordinating sequences of a motor activity, whereas the cerebellum is more important in the fine motor control (*Mendis, 2018*).

Synapses

As previously mentioned, the activation of synapses can result in the formation of new receptors and the enlargement of existing synapses, whereas the lack of synaptic activation can lead to the removal of receptors and the shrinkage of synapses. An increase in the strength of small synapses can cause connected neurons to merge, forming a circuit, which allows memories to be stored. The correlation between the release of transmitters from synapses and the "firing" of action potentials in postsynaptic neurons leads to the strengthening of their connection. In contrast, when the excitatory postsynaptic potential (EPSP) does not reach the threshold potential due to a lack of correlation between the

transmitters and the postsynaptic firing, there is a weaker connection, or it may disappear completely. This behavior is exhibited by all glutamatergic synapses in the mammalian brain, which are referred to as Hebbian synapses after neuropsychologist Donald Hebb, who proposed a similar mechanism in 1949 (*Kennedy Mary B, 2016*).

Neuroglia: Astroglia

Neuroglia are a type of cell that provide structural support to nervous tissue. Astroglia, or astrocytes, are a subtype of neuroglia which are found in the central nervous system. They have other functions as well, such as ensheathing axons and helping maintain isoionia in the extracellular space (*Ota et al, 2013*).

Among the types of neuroglia, astroglia are stellate-shaped, and they contain many processes, which differ in shape and size depending on whether they are supporting white or gray matter. Whether they are in white or gray matter also differentiates them into fibrous and protoplasmic astrocytes. All astroglia contain the glial fibrillary acidic protein (GFAP), which helps in forming glial filaments (*Ota et al, 2013*).

Protoplasmic astrocytes contain short, highly branched processes and are located throughout gray matter. They encircle blood vessels to form the blood barrier, called the glial limiting membrane. Adjacent astroglia may carry out mutually exclusive functions as their domains (around 100,000 synapses in mice) are not overlapping. These functions include the clearance of glutamate, moderation of local blood flow due to changes in synaptic activity, and playing a role in the formation and removal of synapses (*Tabata Hidenori et al, 2015*).

Fibrous astrocytes are mainly found in white matter, and have long, straight processes. While all astroglia contain glial fibrillary acidic proteins (GFAP), they can be found in higher quantities within fibrous astrocytes. The function of these astroglia is not yet known, however they are associated with blood vessels, much like their protoplasmic counterparts (*Tabata Hidenori et al, 2015*).

Among the typical functions of astroglia are, supporting the structure of neural tissue, forming diffusion barriers around synapses, and absorbing extracellular potassium ions for the maintenance of isoionia. They are also able to proliferate to form a scar should there be an injury to neural tissue. Astrocytes are also capable of phagocytosis (*Ota et al, 2013*).

The role of astroglia in long term potentiation by releasing and regulating gliotransmitters is what plays an important role in memory formation through its effects on synaptic plasticity and LTP. Among these molecules are:

- glutamate
- ATP
- cytokines
- D-serine

- adenosine
- lactate

The release of gliotransmitters by astroglia depends on the intracellular calcium (Ca^{2+}) ion level. The neurotransmitter receptor, together with the G-protein coupled metabotropic receptor (GPCR) and G-protein G_q, work to activate phospholipase C, which then degrades phosphatidylinositol 4,5-bisphosphate (PIP_2) into 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). Once PIP_2 is degraded, the endoplasmic reticulum can release its stored calcium ions, which in turns leads to the release of gliotransmitters by the astroglia. This gliotransmission is done through exocytosis of vesicles consisting of the necessary gliotransmitters (*Ota et al, 2013*).

Lactate is one gliotransmitter that is especially important in the regulation of long-term potentiation through its effects on postsynaptic neurons. Astrocytes are able to release lactate to neurons after undergoing the process of glycogenolysis. Neurons need this lactate from astrocytes to use as energy (*Ota et al, 2013*).

Glutamate is another important gliotransmitter in synaptic regulation. The majority of glutamate found between neurons gets removed by astrocytes through metabotropic glutamate receptors (MGluR), NMDA receptors, and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. NMDA receptors are typically expressed on cortical astrocytes, but in the case of astrocytes in the hippocampus, AMPA receptors are usually present. Through the regulation of the release of glutamate, astrocytes are able to promote or lessen the communication between neurons. Increased glutamate levels lead to the expression of NMDA receptors on the presynaptic part of the hippocampal synapse, which in turn leads to promoted communication among neurons. D-serine is also another regulator of these NMDA receptors. Metabotropic glutamate receptors (MGluR) are expressed by astrocytes as well. The most important ones found in hippocampal astrocytes are the mGluR1, MGluR3, and MGluR5 receptors. The release of glutamate is also regulated by ATP. Upon release of ATP by astrocytes, glutamatergic transmission can be controlled, and the expression of AMPA receptors can be increased (*Ota et al, 2013*).

Through ephrin signaling, astrocytes can stimulate the release of D-serine. EphrinB3 is a type of ephrin receptor that is actively expressed by astrocytes during long term potentiation. EphrinB3 receptors are able to regulate the activity of the serine racemase enzyme, an enzyme which can convert L-serine into D-serine. D-serine is a gliotransmitter that activates NMDA receptors (*Ota et al, 2013*). During a study conducted on mice, it was found that blocking D-serine using NMDA D-serine site blocker 5,6-chlorokynurenic acid blocked long-term potentiation (*Ota et al, 2013*).

Astrocytes in Neuropathology

Astroglia may become reactive as a result of inflammation and injuries. Once reactive, they can have an effect on the intake of neurotransmitters, potassium ions, Ca^{2+} signaling, and ion buffering. The changes to the capacity of astrocytes to carry out their functions can have an effect on neurological pathologies such as Alzheimer's disease, Huntington's disease, ischemic stroke, and epilepsy (*Rossi and Volterra, 2009*).

Alzheimer's is a neurodegenerative disease based around amyloid-B (Aβ) aggregation in vessel walls (plaques). It is associated with the loss of synapses. Astrocytes play a role in protection as they take up and degrade amyloid-B, however as the disease progresses, there is a decrease in clearance by the astrocytes. As the amount of amyloid-B increases, a positive feedback is created where astroglia are stimulated to produce pro-inflammatory mediators (*Siracusa et al, 2019*). Amyloid-B has been seen to bind to certain receptors on the surface of astroglial cells. SCARA-1 (scavenger receptor A-1) and MARCO (macrophage scavenger receptor with collagenous structure) are associated with amyloid-B clearance and an anti-inflammatory response respectively. CD36 (cluster of differentiation 36) and RAGE (receptor for advanced glycation end products) are scavenger receptors which are affiliated with the effects of Aβ. Once bound to amyloid-B, CD36 creates a complex with certain toll-like receptors activating an inflammatory response (*Stewart et al., 2010*). RAGE, in the presence of Aβ, produces proinflammatory modifications to the astrocytes themselves. It also has a mediatory effect on the phagocytic properties of the astrocytes as well as its interactions with ligands, namely S100β, which has neuroinflammatory effects (*Cirillo et al., 2015*). A common feature of Alzheimer's disease, S100β, results in depressive behaviors, affects cognitive flexibility, and regulates neuronal oscillations (*Siracusa et al, 2019*).

Astrocyte Activation for Memory Enhancement

There are multiple ways to determine the importance of astrocytes in memory formation. In this study, they tested whether astrocytic activity is enough to initiate synaptic potential and enhance memory. This was established through expressing G_q-coupled receptor hM3Dq in CA1 astrocytes. The CA1 region of the hippocampus is proven to be involved in contextual memory. hM3Dq is a modified version of human muscarinic receptor and is involved in the G_q signaling pathway which releases IC calcium channels and excites neuronal cells. hM3Dq receptor is activated by clozapine-N-oxide (CNO) and through expressing this G_q-coupled designer receptor in CA1 astrocytes, neurons in this region demonstrated learning-dependent potentiation. hM3Dq activates astrocytes upon CNO application as it triggers IC calcium increase in hM3Dq-expressing astrocytes showing that hM3Dq and Ca^{2+} can be used as markers for astrocyte activity. Astrocyte activation is necessary for synaptic plasticity and enhances memory allocation in vivo and memory recall (*Gerlai et al, 1995*).

In addition, the study continued by patching a single astrocyte and monitoring its activity through releasing Ca^{2+}. Calcium release in astrocytes combined with postsynaptic depolarization induces long-term potentiation. Not only do astrocytes encapsulate and insulate synapses, but they also actively sense and modify synaptic activity which works in

memory formation. The study went further to explore the role of astrocytes in synaptic plasticity and memory performance. By inducing NMDA-dependent de novo long-term potentiation in the hippocampus, astrocytic activation increased spontaneous vesicle release and de novo synaptic potentiation.This resulted in enhanced memory allocation and improved cognitive performance (*Gao et al, 2018*).

In the hippocampus, a short-term action potential is only transmitted in postsynaptic neurons as a result of a stimulation of a non-NMDA glutamate receptor. This is only due to a single or unintensive stimulus on the presynaptic neuron. However, intensive or longer-lasting stimulation of the presynaptic neuron leads to extended stimulation of the aforementioned non-NMDA receptor. This disinhibits the NMDA receptor from its magnesium-caused inhibition and allows the flow of sodium and calcium ions into the postsynaptic neuron. This results in more frequent action potentials and also retrograde signals between the presynaptic and postsynaptic neurons, leading to longer-lasting activity and long-term potentiation.

Conclusion

Throughout the research process, we were able to conclude that astrocytes play a crucial role in memory formation of the brain. Astrocytes are neuronal cells that use synapses to form and recall memories. With the help of many different brain parts such as the hippocampus, amygdala, and prefrontal cortex, memories are able to be stored for short or long term. Many processes and receptors in the brain help initiate and elongate synapses to create connections between astrocytes. From intracellular calcium releasing channels to NMDA-dependent long term potentiation, there is a plethora of evidence demonstrating the importance of astrocytes in memory formation. Referring to the studies mentioned above, it is safe to say that the conclusion that we arrived at was accurate. Astrocytes play a role in memory formation and enhancement.

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