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Cell Communication in Brain for Memory and Cognition

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ABSTRACT

Memory retention is the important topic of study in terms of Neurobiology. Cellular circuits involved in the nervous system is seen to be cordially communicating and establishing a network to transfer and store the data. The most extraordinary property of this cellular community is its ability to undergo adaptive modifications in response to environment, originating from inside or outside the body. Such ability, known as neuronal plasticity, allows long-lasting modifications of the strength, composition and efficacy of the connections between neurons, which constitutes the biochemical base for learning and memory. Neuronal and Non- neuronal cells both are involved in the process of memory. Cellular communication can be through release of chemical or a component or by releasing some biological structures like Extracellular vesicles. Also certain hormones are released by cells as a mean of communication and these hormones or cytokine like factors also assist in memory building process. We will further also see the action of these non- neuronal cells when implanted into a mice to check its memory retention.

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Introduction

Cellular communication is important for a proper functioning of the body. All cells need to communicate and respond at the same time for a process to work unanimously. Cells communicate either directly by establishing a contact amongst them or by means of chemical exchange [1-6]. A donor cell under specific conditions or in response to the environment synthesis certain chemical substance that is released in the surrounding from where the neighbouring cell takes up the chemical and responds accordingly. Scientists have been trying to decode the science behind the process of memory over 2000 years now. In 2016, British scientists won the largest prize for neuroscience in the world for their work on memory. The first step to creating a memory is called encoding . Encoding is anything that is witnessed by an individual. On a similar note Semantic encoding is to attach meaning or factual knowledge to any of this sensory input. Post encoding the other two aspects in memory are, storage and recalling. At the cellular and molecular level, learning and memory processes are based on the ability of the neural circuits to undergo long-lasting, adaptive modifications of the strength, composition, and efficacy in the connections between neurons which is called as synaptic plasticity [1, 7]. Synaptic plasticity does not depend only on the activity of nerve cells, but relies on the continuous crosstalk between neurons and the non-neuronal cells around them. Astrocytes, in particular, not only cooperate with neurons at the metabolic level, but also have crucial functions in the formation, maintenance, and potentiation of the neural circuits. Like astrocytes, the other glial cells also release molecules that can influence neuronal activity. On the other hand, neurons produce factors that can regulate the activity of glial cells. Astrocytes release molecules like lactate and glutamate for the signalling process and also membranous structures like extracellular vesicles. Neurons as well as glial cells are known to be releasing EVs that play different roles throughout the process of memory and cognition. In terms of learning and memory, cellular communication and modifying the neural circuits to retain the information is important. Neurons and Glial cells communicate more efficiently and in a cordial fashion. Not just do the glial cells support neurons in return neurons also regulate the glial activity. Cells associated with brains also release hormones like Epinephrine, Estrogen that also play a major role in learning and memory process. The human glial progenitor cells enhanced the synaptic plasticity and learning in adult mice [8-10].

Nervous System and Cells Associated

The Nervous system is the main controlling and communicating system of the body. It comprises a vast network of nerves that send electrical signals called as synapses. These signals are send by specialized cells called as Neurons/ Grey matter. Neurons are excitable cells in presence of stimulating factors. They are surrounded by extracellular fluid (ECF). The stimuli are first received by Dendrites which carries the information/ signal to the cell body that shows presence of nucleus and cell organelles like mitochondria and golgi complex. From there a tube like structure arrives called as Axon which is insulated by myelin sheath. Axon carries the signal to the nerve endings. The region of communication between two neurons is synapse. A synapse is a junction between two neurons. The nerve cell which contributes the transmission and terminal is called presynaptic neuron while other which contributes to the generator region is called post synaptic neuron. Synapse can be electrical or chemical. Electrical current flowing across neurons is the electrical synapse while a chemical synapse involves chemicals called neurotransmitters that are involved in the transmission of impulses.

The Nervous System is divided into two main parts, Central Nervous System (CNS) & Peripheral Nervous System (PNS). The brain and spinal cord constitute the CNS while the PNS is formed from the nerves arising from brain and spinal cord. In addition to neuronal cells the other cells involved in CNS are ependymal cells and glial cells like astrocytes, microglia and oligodendrocytes while the PNS also shows these glial cells in addition to satellite cells and schwann cells. Neurones are responsible for sensing change in their environment and communicating with other neurones via electrochemical signals. Glial cells work to support, nourish, insulate neurones and remove the waste products of metabolism. They are also called as non neuronal cells or Neuroglia and are the supportive cells found both in CNS and PNS. All mentioned glial cells have some role in memory and cognition of while Astrocytes are at prime concern.

Cells in CNS : Ependymal cells, Astrocytes, Oligodendrocyte, Microglia + Neuronal cells
Cells in PNS : Satellite cells, Schwann cells, Astrocytes, Oligodendrocyte, Microglia + Neuronal cells

Astrocyte communication [1-16]

Brain contains small amount of glycogen in astrocytes where it is metabolized and converted to lactate. Astrocytes then release the lactate in the environment and it is taken up by neurons and thereby get activated. At the same time, glutamate as a chemical synapse carrier is released by axons. Glutamate is the main neurotransmitter of brain that carries the signals or associated information across brain cells. Lactate as a hormone from Astrocytes and Glutamate as a neurotransmitter both carry the signals from one astrocyte to the neighbouring astrocyte via a sodium dependent symport mechanism. More recently, it was realized that involvement of astrocytes in neuronal function was even more complex due to their ability to respond to many neurotransmitters and to release a variety of their own signalling molecules (gliotransmitters) thus functioning as regulators of neuronal function. Astrocyte network communicates with the neuronal cells and vice versa thereby establishing a bidirectional exchange of information known as Tripartite synapse. Astrocytes wraps multiple signals at once, due to its broad network various synapse interact with each other and such a interactive transmission occurs through a lateral regulation involving horizontal transfer. Calcium waves elicited by neurotransmitters, neuromodulators, and other extracellular cues, in specific micro domains of the astrocyte network, seem to be fundamental for lateral transmission by astrocytes of a variety of molecules that can modulate neuronal transmission, thus also acting on neuronal plasticity, and even on learning and memory.

Role of Brain derived EVs [1,2,7,11,12]

Apart from molecules like lactate and glutamate, astrocytes also release biological structures called extracellular vesicles which is regulated by the regulatory factor named Neurotrophin BDNF. Extracellular vesicles are membranous structures that comprise exosomes and microvesicles and are known to be released by the plasma membrane of the cells. Both neurons and glial cells release EVs that are means of intercellular communication. EVs transfer molecules like proteins, lipids and nucleic acids. Extracellular vesicles are of different types (microvesicles, exosomes and apoptotic bodies) each having a peculiar function in communication. Two cells establish communication when a donor cells releases EVs which are directly fused into the plasma membrane of the recipient cells. Upon entering the recipient cell, these EVs release the content in them thereby signalling the cell to in-act like the donor cell and respond accordingly . This transfer is involved both in development and proper functioning of the Central Nervous System. Along with glial EVs , neuronal EVs also regulate synaptic activity by communicating with the glial cells and using glutamate neurotransmitter. This thereby displays a trans synaptic communication of information that is captured by memory regulating molecules secreted by EVs across the brain cells.

Like astrocytes, the other glial cells are also able to release EVs. Oligodendrocytes constitute a functional unit with neuronal axons and secrete vesicles containing proteins and myelin lipids in a calcium-dependent manner, in response to glutamate released by neurons. Oligodendrocytes secrete EVs that carry protein and myelin lipids to neurons and regulate their metabolism leading to oligodendrocytes – neuron communication. Microglia release EVs too, and these EVs not only contribute to regulation of the inflammatory response but also participate in regulation of synaptic activity. They also secrete exosomes that is stimulated by serotonin which is another neurotransmitter involved in learning and memory, produced by neuronal cells and regulated by glial cells. EVs released by all the classes of brain cells can play a role of central importance in the CNS as carriers of regulatory signals, some of which are probably involved in neuronal plasticity, learning, and memory.

Hormones Linked to Memory [17]

Epinephrine

One of the best-studied examples of hormonal enhancement of memory formation comes from experiments that examine the effects of epinephrine on memory. Epinephrine is present in chromaffin cells in adrenal medulla and is released into blood from the adrenal medulla in response to arousal and stress and is a classic flight-or-fight hormone.The results show that epinephrine injections after low shock intensity produced strong memories might result from a higher shock intensity in later test trials. The effects of epinephrine on memory follow an inverted-U dose–response curve, where high doses can cause amnesia instead of hypermnesia. The optimal dose of epinephrine resulted in blood epinephrine levels comparable to those obtained by increasing the shock intensity. The generality of epinephrine effects on learning and memory extends beyond task and species. Epinephrine may also contribute to both enhancement and impairment of memory by many treatments. The main evidence for this statement is that peripherally administered adrenergic receptor antagonists, blocking the peripheral effects of epinephrine, attenuate both the enhancing and impairing effects on memory not only of epinephrine but also of treatments such as subseizure and supraseizure electrical stimulation of the brain, analeptic drugs, neurotransmitter synthesis inhibitors, and protein synthesis inhibitors. Thus, epinephrine may be part of a common pathway for the effects of multiple treatments on memory.

Astrocyte and Lactate Contributions to Actions of Epinephrine

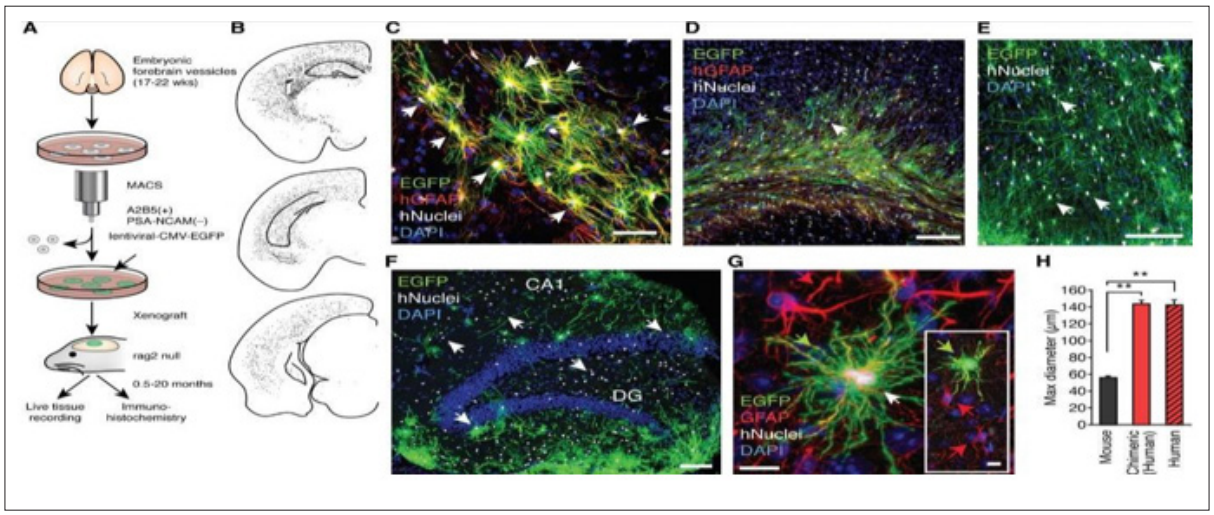
Recent findings suggest that glucose enhancement of memory may be mediated in part by uptake into astrocytes, which can store the energy substrate as glycogen. Glycogenolysis at times of high energy need, including times of learning and memory processing, results in production of lactate for provision to neurons. Evidence supporting this mechanism for glucose actions on learning and memory include pharmacological studies showing that drugs that block lactate uptake into neurons block both glucose and lactate enhancement of memory, while drugs that block glycogenolysis and production of lactate do not block glucose or lactate enhancement of memory; taken together, the results suggest that lactate acts downstream of glycogenolysis. There are several ideas regarding the function of lactate in learning and memory processing. These

include the use of lactate by neurons as an energy substrate, the participation of lactate in providing metabolic support for clearance of neurotransmitters, in particular glutamate, and the vascular signaling by lactate to stimulate blood flow to active brain regions. Importantly, these roles of lactate and glycogenolysis reveal a key involvement of astrocytes in regulating learning and memory processes.

Estrogen

Glial cells in hypothalamus is known to be producing Estrogen hormone in brain. While estrogens are better known for their enhancing effects on memory there is growing evidence that abilities on some cognitive tasks are impaired by estrogen treatment. The direction of estrogen effects depends upon several factors including the stress or age status of the animal and the learning strategy required for optimal task performance. Most notably, acute treatments of estradiol to young adult rats deprived of ovarian hormones through ovariectomy produce impairments in sensory-motor learning that requires rats to learn a turn, ie, right or left, to find food in a maze or to use a cued target to escape water. In these instances, rats with negligible to low levels of estrogens perform quite well. In analogous tasks that require rats to use place or spatial based strategies in which rats use extra-maze cues to guide navigation, the same treatments of estradiol produce enhancements in learning. Moreover, when given an option between response and place strategies within a single task, rats with high estrogen profiles tend to use place strategies while rats with low levels use response strategies. Therefore, both high and low levels of estrogens regulate learning strategy. Learning speed in these dual-solution tasks is similar across rats with different hormone profiles, supporting further the idea that ovarian hormones regulate not only how much, but also what information is acquired. Stress also biases the relative use of different learning strategies, most often producing shifts towards response strategies, and thereby provides additional evidence of convergence between reproductive and stress hormones and highlights the possibility that a broad array of hormones may regulate learning strategy.

Human Glial Progenitor Cells Enhance Memory in Mice [3,4,9,10]



A team of neuroscientists has grafted human brain glial cells into the brains of mice and found that the rodents' rate of learning and memory far surpassed that of ordinary mice. The researchers isolated human glial progenitor cells (cells in the early stages of development before maturing into astrocytes) and labelled them with a fluorescent protein so that the transplanted cells could be identified unambiguously. A suspension of these cells was then injected into the forebrain of new-born mice under anaesthesia. Examination of the brain 2 weeks to 20 months later revealed that mature human astrocytes had apparently inserted themselves into the rodent brain properly, while maintaining their unique human size and shape . A set of standard tests for mouse memory and cognition showed that the mice with human astrocytes are much smarter than their mouse peers. In one test that measures ability to remember a sound associated with a mild electric shock, for example, the humanized mice froze for four times as long as other mice when they heard the sound, suggesting their memory was about four times better. Also in the classic maze test, the mouse with human astrocytes could learn the correct route of maze and crack it in the second try itself. These tests showed that the transplanted astrocytes formed functional channels of communication between mouse astrocytes and other human astrocytes (gap junctions) that enabled them to communicate with adjacent cells and form a large inter-cellular network.

Conclusion

The causal relationship between learning/memory and the ability of the neural circuits to undergo long-lasting, adaptive modifications of the strength and efficacy in the connections between neurons has been now studied for almost 50 years. However it is clearer that both neuronal cells and glial cells communicate with each other to establish a positive outcome of memory retention. Astrocytes, in particular, have crucial functions in the formation and potentiation of the neural circuits. Molecules like lactate and glutamate and also structures like EVs play a crucial role in the process of memory building and cognition. The acknowledgement that both neurons and glial cells release EVs of different kinds, both in physiologic and pathological conditions, is giving us the possibility to explore new routes through which these cells can communicate over long distances with each other. EVs offer a potent tool for studying and explaining at least some of the cellular and molecular mechanisms underlying learning and memory.

Along with organic molecules these brain cells also are known to be releasing hormones like Epinephrine and Estrogen that have a cordial role in memory and cognition. Both the hormones differ in mode of action in cognition and the biological mechanisms by which they act; there are also important common features that should be noted. Each of these hormones can modulate memory,

often enhancing memory. Each of the hormones also includes actions that may be mediated by neurotransmitter release. These hormonal mechanisms may both promote the level of preparedness to change in response to experience and support mechanisms of plasticity needed for those brain changes. Research on introducing human glial cells in mouse showed a positive outcome in terms of response memory and learning suggest that from the already obtained positive results of these cells cultured and multiplied and introduced back into human brain could possibly be an excelling Neurobiology future.

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