.

Memory and factors improving synaptic transmission

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ABSTRACT

Memory is a process that encompasses three basic elements: encoding, consolidation and retrieval. The concept of multiple memory systems is now widely accepted. The question concerning the contribution of new neurons to learning has been recognized for a long time. There are also numerous associations between neurogenesis and learning. Experience-related changes that affect neurogenesis, such as stress or environmental enrichment, also affect learning. This paper also presents some methods of improving memory.
Key words: learning, memory, neurogenesis, synaptic transmission

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Studies of cognition and memory are of interest to many scientific disciplines – neurobiology, philosophy and psychology. Molecular biology and neuroscience however are going to play a central role in coming years.

Memory" encompasses encoding, consolidation and retrieval. Encoding depends on the synthesis of specific proteins in the temporal lobe and hippocampal area – CA_1. This is supported by a growing body of evidence. During learning phase, synaptic activity is at its height and consolidation of memory occurs. Protein synthesis is crucial for the potentiation of synaptic transmission and storage of such information. [1,2,3]

Hippocampus and related structures are involved in various types of memory. [4,5] Clinical research and new studies using modern technology allowed to determine the neuronal oxygen consumption It was thought that memory is a product of many structures of cortical regions of the brain and hippocampus.

Subsequently scientists have shown the existence of several types of memory. [6,7,8] In the early 1980s, the cerebellum was discovered to be essential to learning. Research was conducted both in animals with hippocampal lesion, [9] and in severely amnesic patients. [10,11] In next years, the neostriatum was identified as an important structure of the cerebral cortex for learning and memory habit. [12] Later, it was shown that the amygdala had an essential influence on learning. [13-15] At present, it is widely accepted that no single brain structure is critical for learning and memory processing. Interactions and interconnections with many structures of brain play an important role, particularly with hippocampus, in memory, encoding and retrieval. [16,17]

Vargha -Khaden [18] studied young people with anterograde amnesia. It transpired that hippocampus was necessary for remembering ongoing life experiences, but not necessary for the acquisition of factual knowledge. It was considered that medial temporal lobe structures (MTL) were crucial to various kinds of memory. The role of hippocampus in memory, its many variants and its relation to other medial temporal lobe structures, has been determined by Tulving and Markowitsch. [19] Memory processes including encoding, consolidation, and retrieval involve not only hippocampus, the medial temporal lobe, and diencephalic region, but also neocortical region of the brain. This view was possible to accept, thanks to the adoption of neuroanatomical and behavioural research, using technical innovation and methods like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Owing to the use of those methods and scans of the horizontal sections through the brains of patients suffering from head injuries, it was possible to evaluate the metabolism of fluorodeoxyglucose in the cerebral area. This study visualised the widespread reduction of glucose metabolism in temporal lobes, as well as in diencephalic region, in the hippocampus, and also beyond hippocampal area. [20] The influence of environmental emotional stress and other psychogenic factors in hippocampal structures with sensory related neocortical regions have been also documented. [21] Patients with memory deficits after heart injures showed the changes in hippocampus and in perihippocampal structures as well. [22-24]

Moreover, mentioned techniques allowed determining the changes in neuronal activity during memory encoding and retrieval, separately, and the correlation of those changes with the cerebral blood flow. [25] A number of studies, showing that blood flow changes in the hippocampal formation and adjacent cortical region in medial temporal lobes, has been widely reported. [26,27] Neuroimaging studies have revealed that temporal lobes, as well as hippocampal region and cortex, are engaged in memory encoding and consolidation. [28] While in retrieval, thalamus and brainstem are engaged together with all medial cortical regions. Thus, an assumption results that the two hemispheres are engaged in the encoding process, whereas the right hemisphere with medial cortical region is engaged in the retrieval process.

The authors have proved that MTL system in mammalian brain comprises the hippocampus and surrounding structures and is linked with neocortical areas with limbic region. All those structures interact together to create correct memory processing. [29] According to newer findings, the rhinal cortex has more important role than hippocampus and amygdala for the acquisition of information and its storage.

A number of different brain structures, which were implicated in the diverse kinds of memory and wide variety of learning, lead to an introduction of the accurate classification of declarative and non-declarative memory. See figure 1. Declarative memory is the kind of memory that is used in everyday language. It refers to the capacity of conscious memory of facts and events, which is impaired in amnesia. It is dependent on structures in the medial temporal lobe, including the hippocampus. This proposal has been firmly established by now. Declarative memory can be divided into episodic memory and semantic memory. Episodic memory is the kind of memory for the remembering of what happened, and where, and when. It requires the participation of brain system - frontal lobes. [30] The various systems can be distinguished in forms of different kinds of information and processes, which lead to the encoding of the information. More definitions for the episodic memory have been elaborated, i.e. awareness of the existence of words, objects, events. Semantic memory is the memory which

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acquires actual knowledge, in other words: 'memory for general facts of the world'. The hippocampus for this kind of memory is not necessary. [31] Non-declarative form of memory is expressed through performance and occurs as modification within specialized performance systems. The notion of multiple memory system has been widely accepted. [7,8] Changing the view on the participation of particular brain structures in memory processes is based on the assumption of functional diversity within and beyond MTL structures which are involved in learning and performance. Described structures play the spatial function in human being.

Today it is known that microstructures of the neurons can take part in the reorganization of function in response to afferent environmental factors, connected with learning and training. The existence of interaction and the interconnection between brain microstructures has a great significance for the memory processes. Neuroplastic processes were called functional plasticity and concern not only alone neurons as the axonal projection trees, but also dendrites, and their spikes. [32,33] Konorski, a Polish scientist, was the first to introduce the notion of plasticity of the neuron to the physiology of brain. [34] The author points out the ability of neuron to the durable functional transformation during the learning and memorizing processes. At present it has been accepted that brain regions show vast ability to regeneration, adaptation, and retrieval. New cells in hippocampus and neocortical regions even in old patients can be detected. [21,35] Recent studies indicate that those cells possess the morphology and physiologic properties of more established neuron. [36] Moreover, they develop synapses on their cell bodies and dendrites, as well as extend axons into the CA3 region, [37] or generate action potentials. [38] This brain plasticity is particularly visualised in stroke patients who regain memory and power in upper/lower limbs after different kinds of training. Moreover, stimulation of the neurogenesis speeds up the therapeutic process and leads to fuller compensation of cognitive function. However, it should be emphasised that neurogenesis may be associated with the information of some, but not all types of hippocampal memories. Intensive rehabilitation and constant trainings lead to the retrieval of the power of speech, and even return to self-dependent life. It is a big chance for a better life after stroke or head trauma.

How to improve memory?

Memory can be improved using three methods: pharmaceutical, food supplements and various forms of memory training. The mental body functions are partly regulated by neurotransmitters - particles carrying information between nerve cells, some of them being a part of the cholinergic system. Conduction takes place in those parts of the nervous system where the acetylcholine (ACh) acts as a neurotransmitter. ACh plays an important role in memory and learning, controls sensory input signals, as well as the muscles. With age, the amount of ACh production reduces, which leads to cognitive impairment. Pharmacological agents can inhibit this process and even prevent its occurrence.

N**ootropic drugs** improve learning and memory consolidation without affecting other parts of the central nervous system (CNS), and are usually non-toxic even at high doses. This group includes i.e. piracetam, aniracetam, fipexide, oxiracetam, pramiracetam, pyroglutamate, vinpocetine and many other new molecules in clinical trials. The mechanism of action of these drugs has not been fully elucidated. Most researchers suggest a direct effect on the cholinergic system in the brain which is a part of the nervous system using ACh as a neurotransmitter. [39] **Piracetam** is used in impaired cognition/memory, seizures (epilepsy), neurodegenerative diseases, ischemic stroke, stress, and anxiety. This compound appears to activate the influx of calcium ions into nerve cells, but this function is questioned in light of the findings that sustained influx of calcium may have a detrimental effect on the neuron. [40] Piracetam and its derivatives interact with numerous receptors in the brain and modulate (stimulating and/or inhibiting) the post-synaptic signals, processes involving neurotransmitters and neurohormones. This action may be the result of an impact on the processes of cognition and behavioural neuroscience. It is suggested that piracetam affects the energy metabolism in the body, including the increased use of oxygen in the brain, increasing the permeability of mitochondrial membranes and the same cell for the particles of the Krebs cycle, and the synthesis of cytochrome b5. Other researchers emphasize its antioxidant properties and increased neurotonic density receptors for acetylcholine in the brain. [41] New research suggests the widespread use of this drug in patients with cognitive deterioration caused by brain ischemia after surgical operations. [42] In combination with other drugs, it causes a significant improvement in motor dysfunction in people with epilepsy. Research shows that this drug is involved in the improvement of colour vision in people aged 19 - 24 years with various injuries of the brain, affecting the microcirculation in the retina and probably acts as a GABA-mimetic drug. [43]

Acetyl-L-carnitine (ALC, ALCAR) is a naturally occurring molecule in the body, taking part in the transport of fats into the mitochondria and production of energy in all cells of the body. ALC is a derivative of choline, both in terms of chemical structure and clinical characteristics. Prolonged administration of ALC in animal studies helped preserve the memory and improved spatial

learning. ALC may also have important properties which protect the brain from aging. Acetyl groups stimulate the body to produce acetylcholine, which also affects the secretion of dopamine - a neurotransmitter responsible for mood, thought processes, motor coordination and resistance to stress. It also maintains normal levels of nerve growth factor (NGF), responsible for the proper functioning of neurons. ALC as an effective activator of various physiological processes in the brain tissue also has a direct impact on the functioning of energy conversion in the nerve cells. Effect of ALCAR and its derivatives on memory, learning, and synaptic functions of the brain, have been tested in rats by Kobayashi and colleagues in 2010. These studies confirm that ALCAR increases synaptic neurotransmission in the brain, and thus improves learning. [44]

Few studies previously evaluated the effect of **caffeine** on synaptic plasticity, but the available reports were based on very high concentrations of caffeine, while the concentration achieved by regular consumption of coffee in human brain varies within the low micromolar values. In these values caffeine exerts its pharmacological properties, mainly through the antagonistic action in relation to the adenosine receptor. Caffeine is a non-selective adenosine receptor antagonist, attenuates the frequency-induced LTP (long term potentiation) in the hippocampus in a manner similar to the selective adenosine A2A receptor antagonist. This effect is proposed as the beneficial effect of caffeine in a cognitive abilities reduction associated with aging. [45] Most biological effects of caffeine result from its antagonistic action in relation to all types of adenosine receptor (AR), such as A1, A2A, A3, and A2B, and like adenosine. It has an effect on neurons and glial cells in all areas of the brain. As a result, caffeine acts in opposition in relation to adenosine receptors. Furthermore, caffeine inhibits phosphodiesterase (PDE1, PDE4, PDE5), facilitates the release of calcium from intracellular stores, interacts with the GABA-A receptor, affects brain functions such as sleep, cognition, learning, and memory. [46]

One of the most discussed aspects of aging is the accumulation of lipofuscin in the cells of the brain, heart and skin. In animal studies, reduced lipofuscin accumulation was correlated with improved learning ability, and conversely, increased lipofuscin deposits were correlated with decreased ability to learn. **Centrophenoxine** removes lipofuscin deposits, improves conduction in synapses, facilitating the transfer of information from neuron to neuron. It has been proven that it protects the brain of animals with hypoxia, which may be valuable in some stroke cases and dementia - situations where tissue oxygenation is reduced. On the basis of recent studies, **centrophenoxine** treatment is able to restore the activity of enzymes such as hexokinase, lactate dehydrogenase and dependent on Mg^{2+} ATPase, in the brain and cerebellum. [47]

Recent studies have shown that, isolated from soy, **lecithin phosphatidylserine** compound (transphosphatidylated phosphatidylserine, SB-TPS) reduces memory disorders associated with age. The study was conducted in rats using the Morris maze test. Outcomes shows that SB-TPS increased release of acetylcholine, and the synaptosomes isolated from these rats corresponded with synaptosomes of young rats. Several studies assess the influence of **lecithin** on lipid peroxidation (MDA) parameters, the contents of glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT). The results showed that increased lipid peroxidation in the brain accompanied by drop in activity of antioxidant enzymes, with the same level of GSH. Lecithin, alpha-tocopherol, and their combination improved MDA and CAT activity, with a tendency to normalize the activity of SOD. This fact allowed the authors to conclude that lecithin has a neuroprotective effect in part through its antioxidant properties. [48,49]

Emerging evidence indicates that the beneficial effects of **statins** extend to the central nervous system. Statins have been shown to improve the outcome of stroke and traumatic brain injury, and have been associated with a reduced prevalence of Alzheimer's disease (AD) and dementia. Results of the last research demonstrate that a prolonged *in vitro* **simvastatin** treatment for 2-4 hours, but not a short-term 20 minutes exposure, significantly increases the magnitude of LTP (long term potentiation) at mice synapses. In rat models, chronic administration of atorvastatin or simvastatin, following traumatic brain injury, improves rehabilitation of spatial memory, [50] reduces inflammatory cytokine production, and improves cerebral blood flow to the injury site. [51] Furthermore, neurogenesis in the dentate gyrus, angiogenesis and neurite outgrowth [52] are stimulated by chronic ($\geq$ seven days) statin treatment.

Microelements deficiency can affect memory function, and contribute to cognitive dysfunction and age-related dementia. Trials (assessing the impact, mechanism of action, and safety of **B vitamins)** conducted by Balk and colleagues, among people with Alzheimer's disease (AD) and in patients with Parkinson's disease (PD), show that vitamins B1, B2, B6, B12 and folic acid have neurocognitive functions, and are useful in the diagnosis of AD or in conditions of deteriorating PD. The mechanisms of action have been evaluated in animal and in vitro studies. In animal studies, lack of vitamin B1 or folic acid caused neurological disorders, and supplementation with vitamins B6, B12, and folic acid improved neurocognitive

function. [53] However, administration of vitamin B12 together with folic acid in patients with AD or PD did not provide an improvement in cognitive function [54]. Neuropsychiatric disorders including seizures, migraines, chronic pain and depression are associated with lack of vitamin B6. Epidemiological studies indicate that very low levels of vitamin B6 occur especially among the elderly (with hyperhomocysteinemia). It is suggested to be the cause of the development of Alzheimer's disease and other forms of dementia. The authors have shown that supplementation with B vitamins lowers homocysteine levels in the blood.

Phosphatidylserine (PS) is a naturally occurring component of biological membranes. Mainly it takes part in determining the surface potential of neuronal membranes and participates in the regulation of its ionic environment. As a component of the membrane, it plays a special role in the communication between neurons. With aging, the neuron membrane composition is changed, and loses the ability to transfer electric charge. The receptors are lost, and those remained are of limited functional capacity. PS prevents this process. In addition, the body is involved in activation of protein kinase C (PKC), and this plays an important role in learning and memory. [55]

Vinpocetine (VP) increases blood flow to the brain vessels, as well as accelerates and increases glucose uptake in the nerve cells. Szakall and colleagues conducted research among people after stroke, based on the technique of positron emission tomography (PET). Results showed an increased glucose uptake in brain tissues that have been damaged. [56] In addition, reducing the flow of oxygen (due to decreased blood flow) can significantly damage neurons. Neuroprotective effects of vinpocetine have also been noticed by Rischke and Kregstein, who examined hippocampal damage in rats, seven days after experimentally induced ischemic stroke. In the control group 77% of hippocampal neurons were destroyed, while in patients treated with vinpocetine (10 mg/kg) damage has been reduced to thirty seven percent. [57]

Memory Training

Neurobics - otherwise known as the brain fitness, are special exercises performed and repeated in order to develop and improve memory and intelligence. Neurobics assumes that the brain can be trained and developed, which results in some improvement in various skills, especially memory. It can be assisted by a computer program, containing games and exercises that increase short-term memory capacity or ability to perform calculations in memory [58]. It is also known as neuro-feedback, biofeedback EEG, mind feedback, brain feedback, cerebro-feedback, neurological biofeedback, rehabilitation of the brain, brain training. No side effects of these exercises have been reported as yet. This method can be helpful in a wide range of disorders: attention deficit hyperactivity disorder (ADHD), dyslexia, dyscalculia, anorexia, abnormal behaviour, impaired concentration, sleep disorders, migraine, chronic pain, aphasia, memory disorders, psycho-somatic disorders, anxiety, stage fright as well as a more serious neurological disease/brain damage following stroke or epilepsy. This method is popular with artists, businessmen, managers who seek novel methods of improving concentration, memory, motivation and reducing stress, fatigue, anxiety as well as stage fright.

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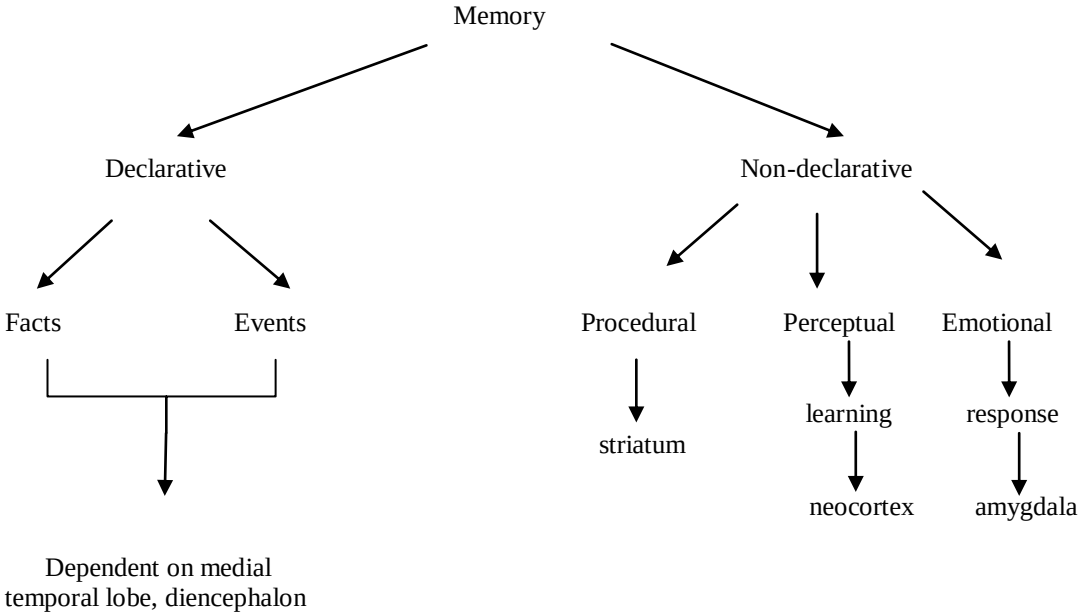

Figure 1. Memory system and brain structures responsible for various forms of memory [28].