The Influence Of Immune Processes On Neurogenesis, Learning And Memory

EMA BOKULIĆ, SONJA MIKULEC
UNIVERSITY OF ZAGREB SCHOOL OF MEDICINE

DOI: http://dx.doi.org/10.17486/gyr.3.1017

SUMMARY: It has long been considered there is no immune activity in healthy brain due to intact blood-brain barrier (BBB). This changes only when it is disrupted by trauma of infection. The latter promotes secretion of pro-inflammatory cytokines by immune and neuronal cells that in turn cause neuroinflammation. In quiescent conditions these cytokines together with prostaglandins, the hypothalamic-pituitary axis and the sympathetic nervous system facilitate processes of neuroplasticity, memory consolidation and neurogenesis. However, this beneficial effect easily turns to harmful one when the immune system is strongly activated. This activation, especially if it becomes chronic, leads to impaired hippocampal neurogenesis, inhibits the formation of LTP and causes memory disturbances. New evidence support the hypothesis that immune processes play an important role in pathogenesis and clinical manifestation of several diseases, AIDS and Alzheimer's disease being one of the most researched. This research gives hope to finding a effective cure or prevention of these diseases.

KEYWORDS: AIDS, Alzheimer's disease, Blood-brain barrier, Cytokines, Learning, Memory, Neurogenesis

Blood-brain barrier and immune system

Blood-brain barrier (BBB) is a diffusion membrane consisting of endothelial cells, astrocyte end-feet and pericytes. It limits excessive interaction between CNS and the periphery, immune system being an important part of it [1]. One of the key components of the barrier are tight junctions between endothelial cells which make it impermeable to large molecules and cells circulating in the bloodstream [2]. [Fig. 1.] Moreover, it is thought that immune-cell activity in the brain is also restriced by constitutive expression of different ligands on neurons, which induce cell death by apoptosis (Fas-ligand nad TRAIL, members of the TNF-alfa super family)[2]. It is proposed to actually consider BBB as a system of parallel barriers – vascular BBB; choroid plexus as a blood-cerebrospinal fluid barrier and the tanycytes which form a barrier around circumventricual organs (third brain ventricle). All of them, in their own specific manner regulate and restrict efflux of the sustances between the blood and the tissues[1].
It was long thought that immune-cell activity does not occur in healthy brain, only under inflammatory conditions such as infection or sepsis that cause BBB disruption. However, it is now believed that BBB disruption is linked to various neuroinflammatory events such as multiple sclerosis, neurotrauma, vascular dementias and stroke [1].
Additionally, some of the studies showed that 80% of the cells present in the cerebrospinal fluid of a healthy individual are memory T-cells (CSF) [2]. There are T-cells specific for CNS antigens that have a neuroprotective role following brain injury although they might also lead to autoimmune disease if their response is exaggerated. Under quiescent conditions their autoimmune activity is supressed by CD4+CD25+ regulatory T-cells but can be activated by a 'danger signal', e.g. brain injury. When such a signal is transmited, it activates antigen presenting cells (dendritic cells and microglia in the brain) which then interact with disinhibited CNS-specific T-cells. As a consequence, those activated T-cells secrete neurotrophic factors that induce microglia to exhibit a neuroprotective phenotype [2].

Neuroplasticity and immune system

Neuroplasticity is an ongoing process in the brain which makes sure that neural circuits that undergo changes are efficiently functioning, accurate and fine-tuned[3]. It involves neuronal apoptosis, degradation of both processes and individual synapses thus leaving debris that may interfere with normal functioning if not cleared out. Therefore, adequate activity of immune mechanisms is crucial for proper efficiency and functioning of these processes. Furthermore, it is suggested that immune-mediated brain remodeling processes are essentialy triggered by neuronal activity. They involve non-neuronal cells within brain parenchyma (mainly microglia, but also astrocytes and possibly mast cells) and endothelial cells, perivascular macrophages and T cells that are a part of brain vasculature, choroid plexus and meninges, as well as complement system and molecules that are a part of major histocompatibility complex class I (MHC-I)[3].

The influence of T-cells, cytokines and prostaglandins on learning and memory under quiescent conditions
As above mentioned, CD4+ T-cells directed toward a brain antigen can be neuroprotective. It is believed that T-cells are situated in meningeal spaces. Experiments on mice with SCID (severe combined immune deficiency, deficient in both T and B cells) and nude mice (deficient in mature T cells) showed impairments with hippocampal dependent memory and learning. What is more, if nude mice or SCID mice were injected with T cells derived from WT (wild type) mice or received bone marrow transplantation respectively, their memory and learning was improved. In addition, one study displayed there is an

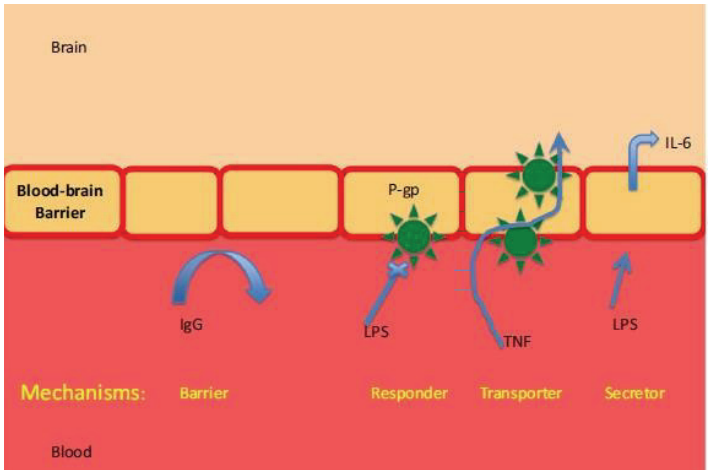

Fig. 1. One of the key components of the barrier are tight junctions between endothelial cells which make it impermeable to large molecules and cells circulating in the bloodstream. (reproduced from: Banks WA. The blood-brain barrier in neuroimmunology: Tales of separation and assimilation. Brain, Behavior and Immunity. 2014; 44: 1-8; http://dx.doi.org/10.1016/j.bbi.2014.08.007)

improvement in learning and memory tests in trangenic mice with excess of brain specific T-cells, unlike transgenic mice with excess of T-cells directed against an irrelevant (non-self) antigen which had worse results in such tests. Alongside these studies on mice, we can observe cognitive impairments related to immune deficiency (including T-cell decrease) in certain common cases – aging, HIV infection and chemotherapy. Furhtermore, it may be possible that boosting T cell immunity by physical exercise and calorie restriction could lessen cognitive impairment that come with aging[3].

Under quiescent conditions, level of produced IL-1 is very low, even below the threshold of detection. Studies showed that IL-1 levels increase during learning process and if a low dose is applied there is a significant improvement in functioning of hippocampal-dependent memory. On the other hand, pharmacological or genetic modification which inhibits IL-1 signaling leads to impaired memory functioning. It is suggested that IL-1 mediates up-regulation of NMDA receptors on hippocampal neurons thus participating in formation of LTP and long-term memory[3].

A study that involved systemic lupus erythematosus and surgical patients showed that high levels of IL-6 have a neuroprotective role on declarative memory impairment no matter the interpersonal differences in age, gender, pain experienced or baseline ability[3].

Although their is ample evidence that TNFα has a detrimental effect on memory processes under healthy conditions, certain studies indicate it may have a protective role when brain homeostasis is disturbed[3].

The influence of prostaglandins on memory was studied by peripheral or intracerebroventricular (i.c.v.) administration of either selective COX-2 or non-selective COX inhibitors. The results showed that inhibition of COX-2 caused impairment in spatial memory and non-selective COX inhibition caused contextual fear memory impairment[3].

Immune processes and modulation of neural plasticity and LTP

It is supported by extensive research that memory formation in hippocampus and other brain areas relies on synaptic plasticity and LTP[3]. When it comes to influence of inflammatory cytokines on LTP, IL-1 seems to have a crucial physiological role on its maintenance. Research on mice reported that IL-1β might have sinergistic effect together with cortisol on memory performance. This is in line with evidence that low levels of glucocorticoids have beneficial effect on hippocampal-dependent memory, neural plasticity and neurogenesis.[3]

Furthermore, there is evidence that endogenous IL-6 may take part in physiological termination of LTP. In vivo studies reported there is an increase in IL-6 gene expression following LTP induction by HFS that also correlated with longer maintenance of LTP.

Moreover, immunoneutralization by administration of anti-IL-6 antibodies showed that IL-6 probably affects maintenance of LTP only in its late phase.[3]

TNFα might not participate in acute plasticity, but rather in processes of long-term plasticity in adult brain called synaptic scaling. It is a process that stabilizes neural networks functioning by modyfing the strengths in all synapses on a cell if change in its electrical activity is prolonged. Moreover, it was found that TNFα involved in that process is secreted only by astrocytes[3]

Lastly, it is suggested that prostaglandins synthesized endogenously by COX-2, not COX-1 could play an important role in promoting long-term hippocampal synaptic plasticity[3].

Immune activity and neurogenesis

In healthy adult brain neurogenesis (proliferation and differentiation of neuronal stem cells) takes place in two locations – subventricular zone of the lateral ventricle (SVZ) and subgranular zone of the hippocampal DG (SGZ). Neurogenesis is considered to be an important aspect of learning, memory and neuronal plasticity most likely because of hyper-plasticity of young neuronal cells in hippocampus[3].

T-helper cells that express a CNS-specific receptor support neurogenesis by producing IL-4 and IFN-γ that activate microglia. In addition, activated microglia produces neurotrophic factors such as insulin growth factor (IGF-1), TGF-β (in adrenalectomized rats), IFN- γ which promote proliferation or differentiation of neuronal precursor cells.[3]

Furthermore, microglia has a high expression of COX-2. If COX-2 is inhibited, neuronal proliferation in both hippocampus and SVZ is reduced by 40-90% which implies that prostaglandins play an important role in neurogenesis, most likely in an indirect way. Another pro-inflammatory cytokine, TNF-α, enhances neuronal proliferation in subventricular zone, but it has no effect on differentiation[3].

Recent studies indicate that astrocytic activity regulates neuronal excitability and synaptic strength by producing various gliotransmiters, facilitates memory consolidation by producing lactate and promotes LTP induction by producing D-serine which binds to neuronal NMDA receptors[3].

It is known that brain derived neurotrophic factor (BDNF) secreted by neurons, astrocytes and microglia affects both neural and behavioural plasticity – hippocampal-dependent memory,

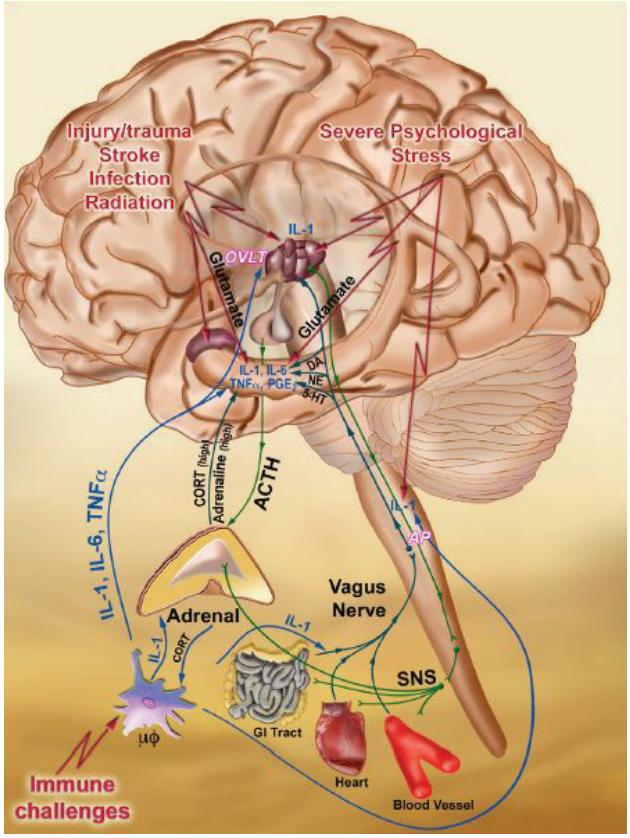

Fig. 2. A systemic model of complex interactions between the brain, peripheral immune cells, the SNS and the HPA axis.
(reproduced from: Yirmiya R., Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain, Behavior and Immunity. 2011. 25, 181-213.)

LTP and neurogenesis. It is suggested that immune activity that involves CNS-specific T-cells and IL-4 stimulated astrocytes induces enhanced BDNF production which in turn has a positive effect on memory and learning[3].

The influence of immune processes on learning and memory under inflammatory conditions

As mentioned before, a delicate balance between neural and immune processes is crucial for brain plasticity, neurogenesis, learning and memory. This delicate balance is easily disrupted by infectious diseases, brain trauma, neurodegenerative diseases, acute or chronic stress. In these conditions, the immune system is strongly activated and complex neural and immune cell interactions occur, resulting in the secretion of high levels of pro-inflammatory cytokines (IL-1, IL-6 and TNFα). Peripheral autonomic and sensory nerve fibers which surround immune cells secrete neuropeptides such as corticotropin releasing factor (CRF) and substance P (SP), initiating the immune response. These immune cells (e.g. the mast cell) are then incited to secrete pro-inflammatory cytokines[4]. When these cytokines are secreted in various parts of the brain, they induce further cytokine production in microglia and astrocytes. Moreover, this "cytokine storm" arising from the brain and peripheral immune cells activates the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic nervous system (SNS), resulting in elevated levels of cortisol, adrenalin and strong activation of brain monoaminergic pathways. Altogether, these processes cause impairments in neurogenesis, learning and memory. [Fig. 2.]

Several experiments, mostly in rodents, were carried out to assess the influence of immune activation on some forms of learning and memory. The results of such experiments should be interpreted cautiously, because many of the symptoms exhibited may be a part of general sickness syndrome, rather than the result of a specific detrimental effect of the immune process on learning or memory[3]. Paradigms used for the assessment of influence of the immune processes on learning and memory are the water maze test (assesses hippocampal-dependent spatial learning), active and passive avoidance task (also hippocampal-dependent learning) and fear conditioning test (hippocampal-independent)[3,5].

Adverse effects of cytokines and prostaglandins on learning and memory

Most of the experiments focused on the effects of the following cytokines: IL-1, IL-6 and TNFα. We concluded that they can facilitate the processes of learning and memory when produced at basal, physiological levels under quiescent, non-inflammatory conditions. Extensive cytokine production during stress or inflammation easily turns this beneficial effect into a harmful one.

The studies showed that both intracerebroventricular and peripheral application of IL-1β damaged spatial, hippocampal-dependent learning in the water-maze test. Similar impairments in hippocampal-dependent spatial and long-term contextual fear memory were found when the effects of chronic transgenic over-expression of IL-1β were analyzed. These impairments are probably the result of neuroinflammation induced by the elevated levels of IL-1 β. The results of other experiments confirmed the connection between bacterial lipopolysaccharide (LPS) application (which serves as a model of infection) and memory disturbances. This negative effect on memory is again mediated by elevated levels of IL-1β. Administration of IL-1 receptor antagonist (IL-1ra) immediately after LPS suppressed this detrimental effect, which is another strong proof of the essential role which IL-1 plays in processes of learning and memory. Aging and exposure to stressors are also connected with neuroinflammation and elevated levels of pro-inflammatory cytokines, particularly IL-1.

IL-6 is another cytokine which plays a significant role in processes of learning and memory. Increased levels of this cytokine are associated with aging, so it is hypothesized that IL-6 is connected with age-related memory deterioration.

The data collected so far about the effects of TNFα is inconsistent. It may only be concluded that the effects of TNFα on

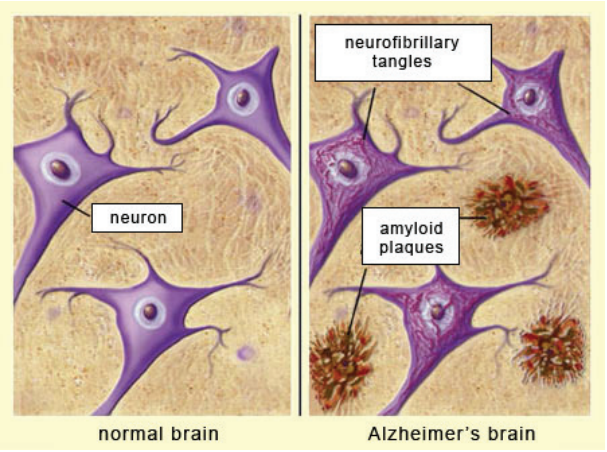

Fig. 3. Neuropathological characteristics of Alzheimer's disease-amyloid plaques and neurofibrillary tangles. (reproduced from: Alzheimer's Disease Research, a program of the American Health Assistance Foundation. http://www.ahaf.org/alzheimers)

memory and learning are apparently dose and age dependent, meaning that TNFα can have both beneficial and harmful effect. The studies which assessed the influence of prostaglandins focused mainly on the effects of the application of COX inhibitors. The results showed that their application had reduced memory impairments caused by conditions associated with neuroinflammation, such as aging, stress, traumatic brain injury, LPS administration[3].

Adverse effects of immune processes on hippocampal LTP and neurogenesis

Infection, brain trauma, stress, natural aging and neurodegenerative diseases inhibit LTP along with memory deterioration. All these states are marked by the elevated levels of IL-1β in the hippocampus, which mediates this inhibition. Moreover, exposure to psychological stress strongly activates microglial cells, inducing the production of high levels of pro-inflammatory cytokines. This excessive, unregulated brain immune activity leads to impairments in learning, memory and neurogenesis that may eventually lead to hyper-excitability, neurodegeneration, excitotoxicitiy and apoptosis. Several studies showed that neural plasticity and neurogenesis are damaged during inflammation due to reduced production of neurotrophic factors or their disturbed signaling[3]. Immune activity may possibly influence hippocampal-dependent declarative and episodic memory through its influence on hippocampal neurogenesis. One study found that the ablation of hippocampal neurogenesis caused by an anti-mitotic drug damaged the rodents' performance in trace eyeblink conditioning[2].

The effects of immune processes on memory deterioration in humans

High levels of pro-inflammatory cytokines were found in autoimmune diseases, such as lupus and multiple sclerosis. One study observed patients with multiple sclerosis, finding that there is a connection between higher levels of IL-6 and poor cognitive abilities. However, research on patients with chronic hepatitis C or type-2 diabetes who usually exhibit moderate cognitive impairments showed no correlation between cytokine levels and memory disturbance. An interesting crossover, double-blind study was conducted in healthy male volunteers. The volunteers were expected to complete psychological questionnaires and neuropsychological tests after LPS or saline administration. LPS had no effect on the physical symptoms of illness, but it caused mild fever and significantly raised the levels of IL-1ra, IL-6, TNFα, and cortisol. Following the intravenous injection of endotoxin, a massive deterioration of memory functions was spotted during all testing periods, which correlated with the production of pro-inflammatory cytokines. On the other hand, the same procedure showed that endotoxin administration had enhanced working memory performance (measured by the Digit Span Backward Test). This enhancement was mediated by changes in cholinergic transmission, rather than cytokine secretion[3].

Another experiment was carried out to assess the influence of peripheral inflammation on human spatial memory. 20 healthy male volunteers went through fluorodeoxyglucose positron emission tomography (FDG PET) scanning before and after typhoid vaccination or saline control administration. After each scanning session, participants had to complete a spatial and procedural memory task. FDG PET scanning sessions revealed an acute reduction of glucose metabolism in the medial temporal lobe (MTL) after the inflammation. The inflammation damaged spatial, but not procedural memory, showing that the inflammation in structures of MTL mediated its effects on spatial memory. The conclusion that peripheral inflammation causes memory impairments could serve as a possible explanation of the pathophysiology of neurodegenerative diseases, most notably Alzheimer's disease (AD). AD shows the same pattern of cognitive impairments like those described in the aforementioned study: MTL-related memory, including spatial memory is damaged, while procedural memory is preserved[7].

Alzheimer's disease as an example of complex interactions between the immune system, neurogenesis and hippocampal-dependent memory

Alzheimer's disease is the most common cause of dementia in elderly people. Neuropathological characteristics are the formation of senile plaques and neurofibrillary tangles. Senile plaques consist of aggregated amyloid beta-peptide (Aβ), while neurofibrillary tangles are intracellular clusters of microtubule-related protein tau. Fig. 3. Recent studies have shown that the immune processes play an important role in the pathogenesis of AD. Inflammatory cytokines like IL-1, IL-6 and TNFα may induce Aβ formation[6]. Amyloid beta then activates microglia to express cytotoxic phenotype which damages neurogenesis [2]. One research demonstrated that treatment with an anti-inflammatory drug, sulindac sulfide in this case, prevented LPS-induced amyloidogenesis, memory impairment and neuronal death in vivo in mice[6]. New studies show that microglia

could have a protective role because it restricts senile plaque formation in murine models of AD[2].

The effect of HIV- caused neuroinflammation on memory and learning

HIV is a neurotropic virus that is transported through BBB either as a free virus by binding via glycoproteins to endothelial surface glycoproteins and transcytosis or within an infected cell through disrupted BBB. Infected immune cells that prevail in the brain during infection are monocytes/macrophages whose activity results in neuronal death and functional loss. When it comes to T-cells there is evidence that lower levels of CD4 T cells are associated with greater neurocognitive decline implying they could have a protective role. On the contrary, there is also evidence they have an important role in pathogenesis of HIV- associated neurodegenerative diseases[8].

Activated HIV-infected monocytes/macrophages and T cells that accumulate in the brain promote neuroinflammation processes which induce astrocytosis and microglial activation. Those processes of neuroinflammation initially take place in the hippocampus, entorhinal and temporal cortices. Furthermore, activated microglia releases neurotoxic substances such as TNF, IL-β, glutamate and quinolonic acid which lead to neuronal damage and cognitive dysfunction[8].

Although antiretroviral therapy successfully suppresses peripheral viral replication the same does not apply to CNS. HIV-1 enhances activation of brain-to-blood transporter thus inhibiting accumulation of antiviral drugs in therapeutic levels. It is suggested that constant, even low, viral activity in the brain causes neuroinflammation and leads to neurocognitive decline[8].

Conclusion

Although neuroimmunology is nowadays one of the most interesting topics in neuroscience, further research is needed to fully understand the complex interactions between the brain and the immune system. This research should especially concentrate on finding the possible pathophysiological mechanisms of neurodegenerative diseases such as Alzheimer's disease. Ample evidence suggest the protective role of anti-inflammatory agents, giving hope to finding a cure or effective prevention of this disease. Furthermore, with AIDS being one of the biggest public health concerns, new research should focus on finding the antiretroviral drug which will successfully inhibits viral replication in CNS, preventing neurocognitive decline.

LITERATURE:
1. BANKS WA. THE BLOOD-BRAIN BARRIER IN NEUROIMMUNOLOGY: TALES OF SEPARATION AND ASSIMILATION. BRAIN, BEHAVIOR AND IMMUNITY. 2014; 44: 1-8; HTTP://DX.DOI.ORG/10.1016/J.BBI.2014.08.007
2. ZIV Y, SCHWARTZ M (2007) IMMUNE-BASED REGULATION OF ADULT NEUROGENESIS: IMPLICATIONS FOR LEARNING AND MEMORY. BRAIN, BEHAVIOR AND IMMUNITY 2008; 22:167-176; DOI:10.1016/J.BBI.2007.08.006
3. YIRMIYA R., GOSHEN I. IMMUNE MODULATION OF LEARNING, MEMORY, NEURAL PLASTICITY AND NEUROGENESIS. BRAIN, BEHAVIOR AND IMMUNITY. 2011; 25: 181-213. DOI:10.1016/J.BBI.2010.10.015.
4. BLACK, PAUL H. STRESS AND THE INFLAMMATORY RESPONSE: A REVIEW OF NEUROGENIC INFLAMMATION. BRAIN, BEHAVIOR AND IMMUNITY. 2002; 16:622-653 DOI:10.1016/S0889-1591(02)00021-1
5. STANFORD SCHOOL OF MEDICINE. BEHAVIORAL AND FUNCTIONAL NEUROSCIENCE LABORATORY. HTTP://SBFNL.STANFORD.EDU/CS/BM/LM/BML_DELAYFEAR.HTML
6. LEE JW., LEE YK., YUK DY., CHOI DY., BAN SB., OH KW., HONG JT. NEURO-INFLAMMATION INDUCED BY LIPOPOLYSACCHARIDE CAUSES COGNITIVE IMPAIRMENT THROUGH ENHANCEMENT OF BETA-AMYLOID GENERATION. JOURNAL OF NEUROINFLAMMATION. 2008; 5:37 DOI:10.1186/1742-2094-5-37
7. HARRISON NA., DOELLER CF., VOON V., BURGESS N., CRITCHLEY HD. PERIPHERAL INFLAMMATION ACUTELY IMPAIRS HUMAN SPATIAL MEMORY VIA ACTIONS ON MEDIAL TEMPORAL LOBE GLUCOSE METABOLISM. BIOLOGICAL PSYCHIATRY. 2014; 76:585–593 HTTP://DX.DOI.ORG/10.1016/J.BIOPSYCH.2014.01.005
8. HONG S, BANK WA .ROLE OF THE IMMUNE SYSTEM IN HIV-ASSOCIATED NEUROINFLAMMATION AND NEUROCOGNITIVE IMPLICATIONS. BRAIN, BEHAVIOR AND IMMUNITY. 2015; 45:1-12 HTTP://DX.DOI.ORG/10.1016/J.BBI.2014.10.008

Utjecaj imunoloških događanja na neurogenezu, učenje i pamćenje

SAŽETAK: Mozak se dugo doživljavao imunološki privilegiranim organom u kojemu nema aktivnosti imunoloških stanica zbog krvno-moždane barijere koja tim stanicama nije dopuštala ulaz u središnji živčani sustav. Trauma ili infekcija narušavaju tu barijeru te potiču imunosne stanice i neurone na lučenje proupalnih citokina. U mirnim uvjetima ti citokini, zajedno s prostaglandinima, hipotalamo-hipofiznom osi i simpatičkim živčanim sustavom, olakšavaju procese neuroplastičnosti, neurogeneze i konsolidacije pamćenja. U stanjima snažne aktivacije imunološkog sustava taj se pozitivan učinak lako pretvara u štetan. Kada snažna aktivacija imunološkog sustava postane kronična, ona dovodi do otežane neurogeneze u hipokampusu, inhibicije stvaranja LTP-a te uzrokuje teškoće s pamćenjem. Novi dokazi podupiru hipotezu da imunološki procesi imaju važnu ulogu u patogenezi i kliničkoj slici nekoliko bolesti među kojima su AIDS i Alzheimerova bolest najviše istraživane. Ova istraživanja mogla bi pomoći u otkrivanju učinkovite metode liječenja ili prevencije ovih bolesti.

KLJUČNE RIJEČI: AIDS, Alzheimerova bolest, citokini, krvno-moždana barijera, neurogeneza, pamćenje, učenje