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ИММУНОЛОГИЯ И АЛЛЕРГОЛОГИЯ

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TANGO OF NERVOUS AND IMMUNE SYSTEMS

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XULOSA

Nerv va immun tizimlar o’rtasidagi o’zaro bog’liqlik mavjudligi tasdiqlangan. Ammo ko’p yillar davomida neyroimmun o’zaro ta’sir mexanizmlari sirli bo’lib qolgan edi. Texnologiyalar va usullarning so’nggi rivojlanishi sababli ushbu o’zaro bog’liqlikni chuqurroq o’rganish va yangi tafsilotlarni ochish imkonini berdi. Bu erda biz markaziy asab tizimi va immun tizimining o’zaro ta’sirini muhokama qildik va eng yangi mexanizmlarga e’tibor qaratdik.

Kalit so’zlar: *asab tizimi, immun tizimi, sitokinlar.*

РЕЗЮМЕ

Перекрестная взаимосвязь между нервной и иммунной системами были установлены и хорошо задокументированы, Однако на протяжении многих десятилетий механизмы нейроиммунного взаимодействия были плохо изучены. Недавний прогресс в технологиях и методах позволил более глубоко изучить эти перекрестные взаимосвязи и выявить новые детали. Здесь мы обсуждаем взаимодействие центральной нервной системы и иммунной системы и фокусируемся на новых механизмах.

Ключевые слова: *нервная система, иммунная система, цитокины.*

INTRODUCTION

Two systems, nervous and immune, have many aspects in common. For example, both systems can sense and memorize. And it’s not surprising that they have complex crosstalk. It’s well-known that nervous system, just like a conductor, orchestrates other systems, and the immune system is not an exception. During inflammation, brain increases abundance of some types of immune cells, and dampens production of inflammatory cytokines, to fight off infection and keep detrimental effect of immune system at bay. After many years of speculations that cognitive state may influence physical well-being, we are provided with studies which suggest that those speculations are not without a ground. Immune cell were initially considered as unwelcome elements in the brain, however, this concept is being revisited, as it has been revealed that meningeal immune cell play crucial role in brain homeostasis, supporting cognitive functions, such as memory, sociability and psychological well-being.

IMMUNE SYSTEM IN MEMORY, ANXIETY, AND SOCIABILITY

After Medawar et al. published the paper on skin graft transplantation to the brain in the 1948, The concept of brain immune privilege has dominated in scientific society(1). And the presence of immune cells in central nervous system (CNS) was associated with a pathology. As recent studies have revealed the pivotal role of immune system in the function maintenance and homeostasis of CNS, the concept was revisited(2). Experiments on the severe combined immune deficient mice, which lack T and B cells, show that the absence of adaptive immune cells lead to impaired memory, social deficit and susceptibility to posttraumatic stress disorder (3–5).

For example, meningeal T cells were demonstrated to play important role in learning and memory, and their depletion led to impairment of these cognitive functions(3). Notably, it was established that training in Morris water maze (MWM) increased interleukin-4 (IL-4) producing CD4+ T cells in meninges, and memory impairment was evident in IL-4-/- mice(3). Further, irradiated mice replenished with T cells from IL-4-/- donor showed poor performance in MWM compared to irradiated mice replenished from wild type control(3). Authors also have shed light to mechanism underlying the beneficial effect of IL-4 on memory, and it was found that the astrocyte Brain Derived Neurotrophic Factor (BDNF) expression, which is necessary for learning and memory(6), is dependent on IL-4(3). Moreover, IL-4 may effect not only BDNF synthesis but also it’s downstream signaling. As BDNF signaling in hippocampus, a brain region closely associated with memory, were reduced in IL-4Rα deficient mice, however, the reduction appeared only on day 5 after MWM(7). Despite the impaired memory in IL-4Rα deficient mice on day 5, learning capability remained on comparable level to wild

type control up to day 4 (7). Intriguingly, IL-4-/- mice demonstrated increased social activity as they preferred to spend more time with other mice than exploring objects compared to wild type control(4).

Conversely, interferon γ (IFNγ) -/- mice were less keen to interacted with their peers, expectedly, injection of IFNγ restored social activity after 24 hours(4). Furthermore, acutely group-housed rodents had increased IFNγ signature genes in prefrontal cortex, whereas isolated rodents had a dramatic downregulation of IFNγ signature genes(4). Also, transgenic expression of IFNγ in oligodendrocytes improved learning and memory(8), however, suppression of IFNγ in protein kinase R -/- mice rescued memory impairment(9). Overall, these results suggest that IFNγ plays crucial role in social behavior and memory.

Another important player in cognitive functioning is meningeal interleukin-17 (IL-17) producing γδ T-cell(10,11). Short-term memory impairment was observed in IL-17-/- mice and T cell receptor δ (TCRδ) -/- mice, while long-term memory maintained intact10. Accordingly, in IL-17-/- mice, hippocampus expressed less BDNF compared to wild type after short-term memory challenge10. Meningeal IL-17 producing γδ T-cells regulate anxiety-like behavior as well(11). When IL-17a and TCRγδ were depleted in meninges, mice revealed less anxiety level in comparison to control in elevated plus maze test, and a direct injection of IL-17 into cerebrospinal fluid increased anxiety in TCRδ-/- mice and stimulated neuronal activation in medial prefrontal cortex, suggesting that IL-17 is important in regulation of anxiety in homeostasis (11).

Proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor α (TNFα) are well-known for their detrimental effect on cognitive functioning and has been discussed elsewhere(12). Surprisingly, knockout of IL-1 receptor or IL-6, led to memory impairment (13,14). As depletion of endogenous signaling could be a more appropriate model rather than global knockout (15,16).

Together, these studies suggest that a plethora of cytokines in brain are crucial for various cognitive functions (fig.1). Undoubtedly, there are many other brain-cytokine interactions still to be uncovered.

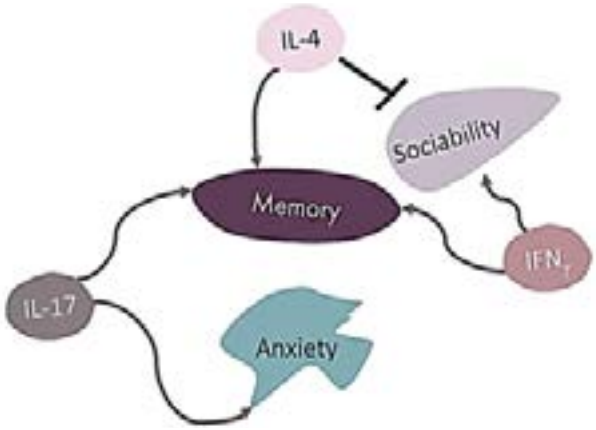

Figure 1. Cytokines influence cognitive functions. IL-4 and IFNγ enhances memory, however, former dampens sociability. In contrary, IFNγ positively regulates sociability. IL-17 plays role in short-term memory, and regulates anxiety.

BRAIN REGULATES IMMUNE SYSTEM.

The influence of CNS on immune system became apparent in the second half of 20 century(17), however, one of the first evidence was documented as early as 1885!(18) Thanks to Pavlovian immune conditioning, a model which was widely used to study the influence of CNS on immune system, many findings were revealed(19). Depending on substance used as an unconditional stimulus, natural killer cells (NK), neutrophils and T cells activity and antibody titer increased after conditional stimulation(20–23). In contrast, when drugs, such as cyclophosphamide and cyclosporine A are applied during acquisition, immunosuppression is elicited at evocation phase(24–27). Despite the abundance of literature on behavioral immune conditioning, its mechanism remains poorly understood (19).

Nevertheless, it was revealed that brain regions, such as ventral tegmental area (VTA), paraventricular nucleus, hippocampus, insular cortex, and amygdala are necessary for neural control over immune system(28–33). For example, hypothalamus regulates B cells, T cell and NK cell numbers at various sites, enhancing anti-cancer defense(34–36). The activation of VTA, which is involved in reward system, boosted monocytes and macrophages number and phagocytic activity in peritoneum, decreasing bacterial load(28). After stimulation of reward system, adaptive immunity was upregulated as well, manifested by the increase of IFNγ+ T cell, B cells and antibody titers(28) (fig. 2). Stimulation of paraventricular nucleus (PVN) and amygdala increased spleen plasmocytes and antibody titers(29) (fig. 2). Also amygdala and insular cortex were necessary for conditioned enhancement of antibody production, however, the lesion of hippocampus didn't disrupt this immune conditioning(37). Interestingly, blockade of IL-1 signaling in hippocampus disrupted

heroin-conditioned decrease of splenic iNOS mRNA and plasma nitrate, which suggests that different brain regions modulate various aspects of the immune system (30).

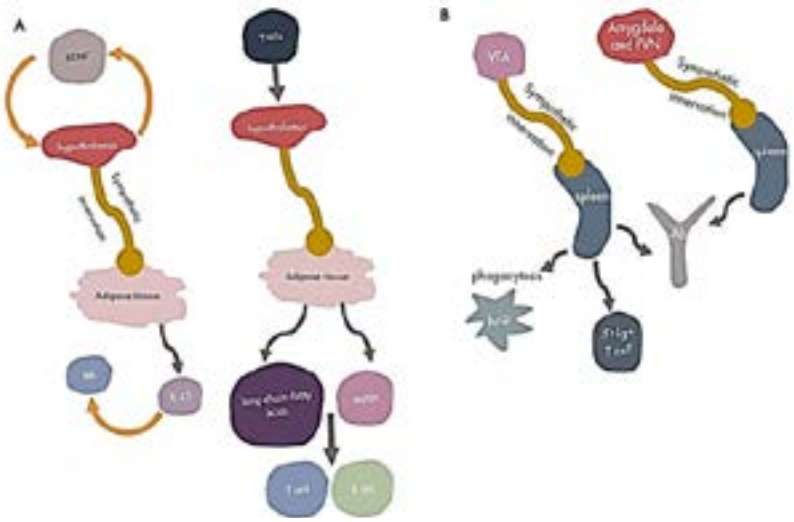

Figure 2. Brain regions enhance immune system via the sympathetic pathway. A. VTA boosts phagocytosis activity, IFNg+ T cell abundance and antibodies titer in spleen . Amygdala and PVN stimulation increase plasmocyte number and antibodies titer in spleen. B. Hypothalamus activates immune cells via adipose tissue innervation. BDNF upregulation in hypothalamus leads to IL-15 synthesis in adipose tissue, which increase NK cell frequency. TNFa signaling in hypothalamus triggers long-chain fatty acids and leptin release in adipose tissue, and consequently to increased T cell and B cell abundance

Recently, mechanisms underlying neural immune regulatory pathways were further elucidated (fig. 2A). It was shown that VTA activates immune system, at least partly, via sympathetic neurons, as its chemical ablation led to disruption of immune stimulation and enhanced bacterial clearance (28). Conflicting with this, surgical sympathetic denervation was shown to dramatically increase bacterial clearance, however these experiments were performed on different hosts (38). By infecting spleen nerves with fluorescent protein-expressing recombinant pseudo-rabies virus, Xu Zhang et al. literally illuminated and elegantly demonstrated the innervation of spleen by amygdala and PVN, confirming it with complement experiments, such as ontogenetic neuron activation and splenic denervation(29). Intriguingly, it was demonstrated that the activation of hypothalamus by TNFa triggered leptin and long-chain-fatty acids release in adipose tissue, increasing T cells and B cells abundance in spleen and adipose tissue(35)(fig. 2B). Surgical sympathetic denervation of fat ablated this boost of adaptive immune response, disrupting brain-fat axis(35). Moreover, BDNF signaling in hypothalamus led to the upregulation of IL-15 synthesis in adipocytes, and consequently increased natural killer (NK) frequency in the context of enriched environment (EE) (34) (fig. 2B). Anti-cancer effect and increased T cells abundance in spleen were observed in mice after housing in EE(36).

Well-known inflammatory reflex, which consists of efferent and afferent vagal arms, senses inflammation by latter and signals to dampen it via efferent neurons(39,40). Stimulation of vagus decrease pro-inflammatory cytokines production, such as IL-1,IL-6, IL-8 and TNF-a(41). Interestingly, electrical stimulation of vagus nerve was shown to increase phagocytosis(42), and surgical vagal denervation dampened phagocytosis(43). Moreover, vagotomy, as expected, led to increased proliferative and cytokine production potential of CD4+ T cells, however, decreased T cell independent antibody production was observed after vagotomy(44,45). Advance in technologies have allowed to further elucidate this anti-inflammatory arc. During inflammation in colon, hepatic vagal afferent sensory nerves translated signals to nucleus tractus solitarius in brainstem, and consequently, left efferent vagal neurons relayed input to enteric neurons, in turn, they stimulated antigen presenting cells and their production of retinoic acid, which is essential for Tregs homeostasis (46) (fig. 3A). As expected, hepatic vagotomy led to worsening of colitis, abrogating this anti-inflammatory liver-brain-gut axis(46). Interestingly, right vagotomy led to poor bacterial clearance, as a result of the reduction of ILC3 and its production of 17-HDHA, a molecule which is further converted into PCTR1 by macrophages(43,47) (fig. 3B). PCTR1was shown to enhance phagocytosis and reduce pro-inflammatory molecules production, such as eicosanoids and IL-8, promoting infection resolution in mice (43).

Taken together, above mentioned studies indicate that brain strongly regulates various aspects of immune system utilizing both sympathetic and parasympathetic pathways.

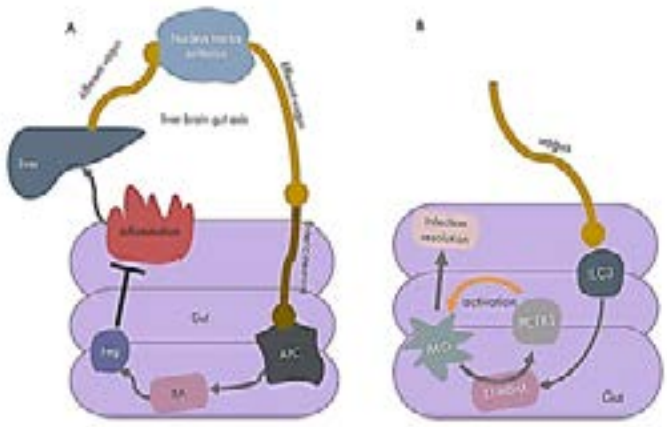

*Figure 3.*Vagus regulates inflammation in gut. A. Vagal signaling stimulates 17-HDHA production by ILC3. Macrophages convert 17-HDHA into PCTR1, which enhances phagocytosis activity and bacterial clearance. **B.** Liver senses inflammation in gut, and signals to brain via afferent vagus. Nucleus tractus solitarius relays signal to efferent vagus, enteric neurons and APC. In response to stimuli, APC produces RA, which is important in Treg homeostasis and prevention of the bowel inflammation.

CONCLUSION

Cytokines, produced by immune cells in meninges, help to regulate and maintain cognitive functions, however, during inflammation, proinflammatory cytokine may flood brain and cause detrimental effect. Neural terminals in periphery or brain centers may sense inflammatory signal and respond to it by dampening proinflammatory cytokine and enhancing immune cells. Studying the neuroimmune dialog is important for understanding the underlying mechanisms of cognitive homeostasis and inflammation resolution. Above mentioned results may pave the way for the development of the new therapies and diagnostic tools. For example, there are studies that demonstrate that positive emotions and expectations and enriched environment boost and recruit immune cells, regulate cytokines and increase defense against infections and cancer (28,34,36,48) it remains unknown whether and how reward system activation affects the body's physiology and, specifically, immunity. Here we show that activation of the ventral tegmental area (VTA. In contrast, depression is a risk factor for the development of inflammatory disease(49). Future studies would further unveil mechanisms of neuroimmune interaction and create new perspectives.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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