Review Article

Immune Tolerance Therapy: A New Method for Treatment of Traumatic Brain Injury

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Abstract

Objective: Due to the special anatomical structure and pathophysiological mechanism of the central nervous system (CNS), there is a big difference between the repair of brain injury and other systems of the body. More and more evidence shows that targetedly reducing the autoimmune response of brain tissue without affecting the immune function in other parts of the body will be the best optimized treatment for brain injury.
Data Sources: This review was based on data in articles published in PubMed up to June 5, 2017, with the following keywords: "immune tolerance", "traumatic brain injury", and "central nervous system".
Study Selection: Original articles and critical reviews on immune tolerance and brain damage were selected for this review. References of the retrieved articles were also screened to search for potentially relevant papers.
Results: The CNS is isolated from the immune system through the blood-brain barrier. After brain injury, brain antigens are released into the systemic circulation to induce damaging immune responses. Immune tolerance can effectively reduce the brain edema and neurological inflammatory response after brain injury, which is beneficial to the recovery of neurological function. The clinical application prospect and theoretical research value of the treatment of immune tolerance on traumatic brain injury (TBI) is worth attention.
Conclusions: The establishment of immune tolerance mechanism has a high clinical value in the treatment of TBI. It opens up new opportunities for the treatment of brain damage.

Key words: Central Nervous System; Immune Tolerance; Traumatic Brain Injury

Introduction

Traumatic brain injury (TBI) is a global burden,[1] which caused about one-third of injury deaths.[2] It is reported that head injury occurs above 1/1000 in China which was caused by increasing traffic accidents.[3] Ziegler *et al*.[4] stressed that about 1.7 million people suffer from TBI annually in the United States in which about 275,000 are hospitalized and 52,000 die. The central nervous system (CNS), especially the encephalon, is isolated from the immune system by the blood–brain barrier (BBB),[5] which provides functional and structural support for the brain. BBB disruption is a common pathogenic feature in many types of brain damage, for example, trauma and surgical brain injury (SBI). Brain edema is a characteristic pathophysiological condition caused by BBB disruption which leads to an excessive increase of brain water content and inflammatory damage. The reasons of these damages are immune cell infiltration and hemorrhage caused by the destruction of the microvascular structure.[6]

Investigations involving the CNS and the immune system led to the belief that brain is an immunologically privileged organ.[5,7] Brain injury can attract immune cells, cytokines,

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chemokines, and other inflammatory mediators to the injury sites. Inflammatory-related mediators can induce neural excitotoxicity, oxidative stress, mitochondrial dysfunction, and increased possibility of secondary inflammation.[8,9] After TBI destroys the BBB, antigens of the brain tissue are released into systemic circulation. Therefore, the severity of BBB destruction can be accurately indicated by detecting the concentrations of S-100 antibody.[10,11] In the process of CNS injury and repair, the immune response was involved without exception. The current research focuses on reducing or enhancing immune responses against brain diseases based on clinical needs. And, the treatment of TBI is focused on reducing the immune response. There are many ways to attenuate the effects of traumatic brain injuries, for example, nonspecific diuretics, anti-inflammatory agents, mild hypothermia therapy, and immunosuppressive agents.[12-14] Although these treatments have advantages for neural protection, they are likely to cause infection and tumors.[12] Therefore, we need to explore new ways to treat brain injury.

Immunological Characteristics

Thymus has been regarded as an intrinsic component of the endocrine system for a long time; however, the cell-to-cell signaling endocrine model cannot be fully elucidated in this organ.[15] Thymus is still believed to be regulated by a mechanism of humoral; however, the function of T-lymphopoiesis was discovered by more and more researches and the endocrine function of the thymus progressively reduced from the literature. A great number of studies indicate that thymus is a crucial area for linking the neuroendocrine and immune systems, especially during fetal development.[16] Thymus is the primary lymphoid organ and produce immunocompetent and self-tolerant T-lymphocytes in the development of immune system. The thymic parenchyma is the site of export of a diverse protein precursors belonging to different neuroendocrine families. Those thymic protein precursors can provide accessory signals during the development of T-lymphocyte; moreover, thymic protein precursors are served as the self-antigens of neuroendocrine which are presented to differentiating T-lymphocyte.[17] Therefore, the interaction between neuroendocrine and immune system is not only the basis for regulating the homeostasis of human body, but also the key condition to ensure the normal development of other species.

To maintain the homeostasis of immune system, the immune system must possess the ability to recognize and tolerate the neuroendocrine self-proteins before being able to react against infectious non-self-antigens. Immune tolerance is only educated in thymus. Thymus dysfunction in producing neuroendocrine-related antigens in the development of tolerance will lead to autoimmune response directed to neuroendocrine glands. Regulatory T cells (Tregs) can decrease the immune response of peripheral tissues to T cells. The dysfunction of thymus could break off the immune homeostasis by proliferating numerous self-reactive T cells and decreasing the number of self-antigen-specific natural Tregs.

It is reported that a numerous neuroendocrine self-antigens are expressed by the thymic epithelium which is controlled by the autoimmune regulator (AIRE) gene/protein.[18] According to a review, numerous gens are expressed in the thymus, including circulatory, central nervous, digestive, and eyes.[19] Myelin basic protein (MBP) is the second most abundant protein after proteolipid protein (PLP) in CNS. Although many studies reported that MBP was in RNA level,[20,21] according to Boggs, the protein of MBP is not expressed in the thymus.[22] The MBP exists in "immunological privileged site" normally.[23] However, when BBB is broken, the autoantigens would leak into peripheral circulation and activate T lymphocytes.[24,25] Besides, the resident immune cells, for example, microglia, could induce autoimmune reaction by presenting autoantigen to T lymphocytes.[26] Therefore, the antibrain antibodies (ABAbs) in serum may be increased after TBI.[27] Inducing immune tolerance to MBP can reduce the occurrence of secondary inflammation and provide neuroprotection after brain injury.[28,29]

Recent studies have shown that the brain has an adaptive immune surveillance characteristic, and there is a classical lymphatic drainage system with specific loci, most of which enter the nasal lymphatic system through the sieve plate, and the normal function of the brain microglia is set to be immune tolerant.[30-34] The self-tolerance protection mechanism of brain tissue can prevent more abnormal brain function due to inflammatory damage, thereby maintaining the stability of brain function.[35] The CNS is extremely sensitive to inflammation and has poor regenerative capacity; thus, limiting the immune privilege of damage is particularly important.[36] The thymus is just like a "school" that educates naïve T cells to tolerate self-antigens and produces different self-tolerant T cell receptors. In other words, T cell repertoire recognizes adventive antigens and is tolerant to self-antigen which is generated early in life in the primary organ for T cell development.[37,38] Thymus is just like a bridge that connects the immune system and the neuroendocrine system. Only 1–2% of T cell progenitors will develop into self-tolerant and will mature after the cells left thymus. In spite of most of the T cell progenitors are cleaned, the mature T cells can defy the non-self-antigens that appeared in the periphery. Therefore, this immune tolerance mediated by thymus is extremely powerful.[39-41] In healthy thymus, self-antigens expressed on the surface of thymic epithelial cells (TECs) determine whether immature thymocytes survive or die. The thymus is composed of two morphologically and functionally different compartments: the cortex and the medulla; they nurture two distinct kind of TECs, namely, the cortical TECs and the medullary TECs.[42-44] Thymic nurse cells (TNCs) are large ECs and contain a large number of internalized thymocytes that are engulfed within caveoles delineated by TNC plasma membrane.[45,46] It is reported that TNCs express Class I and II major histocompatibility complex (MHC) that means TNCs play an important role in T cell development and MHC restriction.[47] TNCs also express the neuroendocrine self-antigens and the AIRE, for example, oxytocin and insulin-like growth factor-2.[48] Therefore, TNCs not only

have an important role in thymocyte development but also demonstrate their importance to T cell tolerance. Although mature T cells come from the thymus where positive selection and negative selection occurred,[49] a part of T cells also react to self-antigens and lead to autoimmunity diseases. This implies that peripheral immune tolerance mechanisms are most important for controlling mature T cells escaped to the periphery and react to self-antigens. To control these self-reactive T cells, several peripheral mechanisms have reported to limit autoimmunity, namely, clone anergy, peripheral deletion, and Tregs.[50,51] According to the research, Tregs are supposed to participate in the inactivation of autoreactive cells and are the cornerstone component for maintaining peripheral self-tolerance.[52]

Brain Injury and Immune Tolerance

Autoimmune diseases have always been the focus of immune tolerance research. According to Getts *et al*.,[53] microparticles bearing encephalitogenic peptides can induce T cell tolerance and mitigate experimental autoimmune encephalomyelitis (EAE). According to Billetta *et al*.,[54] treatment of EAE with a peptide of heat shock protein demonstrated a significant clinical improvement. Immune tolerance therapy has been explored not only in autoimmunity diseases but also in stroke. Takeda *et al*.[55] reported that induction of mucosal tolerance to E-selectin can prevent ischemic and hemorrhagic stroke in spontaneously hypertensive, genetically stroke-prone rats. According to Jellema *et al*.,[56] mesenchymal stem cells can induce T cell tolerance and protect the preterm brain when hypoxia-ischemia occurred. There are so many diseases that can be treated by the "reeducation of specific antigen" and "mucosal immune tolerance" happened in immune center. For instance, intranasal delivery of E-selectin can suppress the atherogenesis after E-selectin tolerization,[57] immune tolerance, and myasthenia gravis;[58] oral antigen tolerance may be used to treat autoimmune inner ear disease.[59] At present, although only a few studies have reported the treatment of TBI by immunotolerance therapy, they are enough to provide inspiration for new TBI treatment.

Brain tissue contains a large amount of autoantigens, such as human brain S100 protein, neuron-specific enolase, and MBP. Once the BBB is broken, these autoantigens would get into the blood. Based on this theory, some researchers[60-64] implied these antigens as serum markers to evaluate the severity and prognosis of TBI. ABAbs are autoantibodies against brain tissue that are produced by the immune system.[65] According to Yan *et al*.,[27] 96 cases (49 cases of TBI and 47 health adults) were phlebotomized and tested with ELISA to observe the changes of ABAbs and they discovered that there was a few ABAbs in the blood serum of health adults and the concentration of post-TBI ABAbs was higher than nature. Analyzing the reasons, in addition to the damage of brain tissue and BBB after TBI, increasing production of brain tissue antigens stimulates the immune system to produce large amounts of ABAb;[66-68] moreover, severe trauma can quickly cause the body's stress response, activate the neuroendocrine system, and mobilize the immune system to participate in stress. At this time, the immune system function can be more hyperactive than normal, easily receiving antigen stimulation and producing antibodies. In the early stage of TBI, immune cells, cytokines, chemokines, and other inflammatory mediators are attracted to injury sites, which induce neural excitotoxicity, oxidative stress, mitochondrial dysfunction, and increased secondary inflammation.[69] Furthermore, high levels of ABAbs may attack brain tissue, aggravating secondary damage after trauma.[27]

Self-cerebrospinal fluid (CSF) contains a large amount of brain antigen components. Yan *et al*.[70] confirmed that enhanced permeability of the BBB and astrocyte growths after injury is the primary means of brain tissue antigens flowing into the blood. In addition to normal function, drainage of CSF can help reduce brain tissue antigen leakage into the blood. As a result, concentration of ABAb reduced and secondary immune brain damage became slight. Fu *et al*.[71] reviewed that immune interventions can reduce edema, apoptosis, and brain atrophy in animal models of intracerebral hemorrhage. These solutions may provide a foundation for clinical application. Therefore, it is a better choice to simply reduce the immune response against brain tissue antigens without affecting the immune tolerance of the immune function of other antigens. Benson *et al*.[72] and Meyer *et al*.[73] found that the clinical symptoms of relapsing EAE could be reduced by oral administration of MBP. Ayer *et al*.[28] successfully induced immune tolerance through instilling autoantigen to the nasal mucosa and found that it had a neuroprotective effect on brain injury.

How to Induce Immune Tolerance

Autoimmune responses involve various immune cells, especially CD4+ T helper cells. CD4+ T cells classically differentiate into two subgroups: pro-inflammatory Th1 cells and anti-inflammatory Th2 cells.[74] Th1 cells mainly secrete interleukin-2 (IL-2) and interferon-γ, whereas Th2 cells mainly secrete IL-4 and IL-5.[75] Cytokines are necessary regulators for lymphocyte trafficking. It is essential to turn an innate immune response into an adaptive response. IL-2 and other cytokines promote cellular immunity and those cytokines are important for attracting CD4+ T cells and CD8+ T cells to the injury site to establish specific immune responses.[76] IL-2 is secreted by activated T cells, especially Th1 cells, and IL-2 itself is an activator of T lymphocytes.[77] Thus, the expression level of IL-2 reflects the degree of activation of Th1 cells. As shown in *in vitro* and *in vivo* studies, IL-2 is capable for breaking immune tolerance.[78] In addition, the central hallmark of anergy is the inability of CD4+ Th1 clones to synthesize IL-2, which results in abortive proliferative responses and a deficit of producing inflammatory mediators, and thus, IL-2 is an effective and complex balancing factor that affects tolerance and immunity.[79] IL-4 is an essential anti-inflammatory factor

and is the characteristic cytokine of Th2 cells that induces the differentiation of Th2 cells.[80] Moreover, Walsh *et al*.[81] indicated that IL-4 mediated neuroprotection and recovery of the injured CNS. T cells serve as a vital part of the immune system, specifically CD4+ T and CD8+ T cells. Yilmaz *et al*.[82] found that cerebral ischemia/reperfusion injury significantly increased the level of CD4+ T cells in cerebral tissue, whereas it decreased the level of CD8+ T cells. Moreover, the CD4+ T/CD8+ T ratio was notably decreased upon drug intervention. Another study also demonstrated that the CD4+ T/CD8+ T cell ratio increased in cerebral ischemia/reperfusion injury sites.[83] In experimental stroke, CD4+ T lymphocytes and CD8+ T lymphocytes contribute to inflammation, brain injury, and neurological deficit. Consistent with these studies, the expression of IL-2 was decreased, and the expression of IL-4 was increased, which indicated MBP and autogeneic brain cell suspensions led to Th1/Th2 deviation and T cells anergy. The above results, combined with the decreased CD4+/CD8+ T cell ratio, are favorable for the establishment of immune tolerance.

Since immune tolerance therapy is an important method to treat brain diseases, it is necessary to introduce the ways to induce immune tolerance. According to the research, preventive induction of Tregs targeting brain tissue has the effect of reducing specific autoimmune responses.[84] Tregs play an indispensable role in maintaining immunological unresponsiveness to self-antigens and in suppressing excessive immune responses deleterious to the host. Tregs have been widely studied which can inhibit the activation and expansion of effector T cells and help induce transplantation tolerance and suppress graft rejection. Furthermore, in the presence of Tregs that actively maintain graft tolerance, naive T cells could be newly recruited to the graft site and could differentiate into graft-specific Tregs, thereby augmenting graft tolerance.[85] The same principle could be applied to the treatment of brain diseases. Mucosal tolerance, liver tolerance, thymus tolerance, and skin-induced tolerance are the most ways to treat diseases.

Mucosal Tolerance

Mucosal tolerance is a widely used method to induce immune tolerance in different diseases. Oral tolerance has been explored by numerous studies and does not respond to an orally administered antigen. Numerous studies reported that oral tolerance can reduce inflammation in the CNS of EAE mice.[86,87] The mechanism of mucosal tolerance is a method of inducing immune tolerance to a specific antigen through chronic exposure of that antigen to the mucosal surfaces of the subject.[88] Tolerance occurs after repetitive low-dose exposure of the antigen to mucosal surfaces (typically oral or nasopharynx surfaces in experimental models). Reexposure of the same or similar antigens to the immune system of tolerant patients results in a modified immune response that is characterized by specific T-regulatory lymphocytes.[88] This specific T cell population secretes cytokines, such as transforming growth factor β1, which suppresses the cell-mediated immune response at the site of antigen exposure or injury.[89-95] Mucosal tolerance to MBP has been previously shown to improve outcomes after ischemic stroke.[84,96,97] Ayer *et al*.[28] reported that the induction of the immune system's tolerance to MBP by the nasal mucosa promptly inhibited the inflammation, reduced cerebral edema, modulated the neuroinflammation after SBI, and then provided neuroprotection. This experiment provides evidence for a unique anti-inflammatory therapy against SBI that potentially avoids many of the pitfalls of other anti-inflammatory approaches. Mucosal tolerance to brain antigens can provide anti-inflammatory therapy in a timely and site-specific fashion.[28] Through mucosal tolerance, it is possible to modulate the immune system's interaction with specific antigens as opposed to suppressing the entire system. Besides the mucosal tolerance, Yan *et al*.[70] found that TBI can lead to the disruption of BBB and cause a large number of brain antigen leakage into the blood, leading to ABAb production. CSF feed by mouth in rabbit-TBI models established by lateral fluid percussion machine can result in oral tolerance, which has therapeutic effect on TBI.[98] The mechanism of immune tolerance depends on antigen presentation to immune cells by immature dendritic cells. Studies have shown that oral immune tolerance can specifically reduce the attack of lymphocytes on brain tissue and protect the injured brain tissue.[98] One of the prime determinants in the successful establishment of mucosal tolerance is the dose of antigen. Low doses favor the induction of Tregs and high doses favor the induction of anergy or deletion.[99] The efficacy of mucosal tolerance is currently undergoing testing in humans for the treatment of rheumatoid arthritis and multiple sclerosis, and no toxicities or autoimmune reactions have been found.[100,101] However, we think that there are some shortcomings in the clinical transformation of mucosal tolerance in the treatment of brain diseases, for example, the individual mucosal absorption rate is uncertain; craniocerebral trauma is often associated with nose and facial injuries, often limiting the use of nasal mucosa antigen; severe TBI or stroke with stress ulcer requires fasting water and gastrointestinal decompression, limiting the use of oral immune tolerance. Therefore, future researches should focus on other immune tolerance therapies for brain injury. The establishment of immune tolerance for the thymus and liver gradually attracted attention.

Thymus Tolerance

Thymus is an organ of the central inmune organ where T cells experience positive and negative selection and prompt Tregs. Immune tolerance can be induced by thymus. Therefore, many studies have reported that intrathymic injections of cells or antigens induce immune tolerance to treat graft rejection.[102-104] Injection of astrocytes in EAE rats induces the proliferation of Tregs to significantly reduce the inflammatory and clinical symptoms of the CNS.[105] Some researchers hypothesized that αB-crystallin, PLP, S100β

protein, and α and β isoforms of myelin oligodendrocyte glycoprotein (MOG) are self-antigens of multiple sclerosis; the expression of the five components in the thymus was observed by real-time quantitative polymerase chain reaction – the results showed that the thymus did not express the MOG – while the other four components were positive in the thymus stromal epithelium and medulla.[106] It suggested that the demyelinating disease was related to the thymocyte intolerance to MOG. The above two studies provide theoretical basis and preclinical experimental support for the intrathymic injection of brain tissue antigen to rebuild immune tolerance. Using some therapeutic techniques or methods to contact central organs (such as the thymus) that produce and promote the maturation of immune cells with pathogenic brain antigens is inaccessible under normal conditions. The immune center recognizes these specific antigens as self-components and forms self-tolerance and does not produce lymphocytes to attack these antigens. At the same time, it still retains immune recognition and attack capabilities against other recognized heterologous antigens. Chen *et al*.[107] reported that intrathymic injection of Ag induces apoptosis of immature thymocytes and a subpopulation of mature thymocytes and induces prolonged anergy in peripheral T cells *in vivo*.

A preliminary study by our group confirmed that immune tolerance can be induced by intrathymic injections of brain antigens. In the animal model of TBI, the injection of self-CSF and self-brain-homogenate into the thymus can induce the immune tolerance of brain antigen, which has therapeutic effect.[12,108,109] We then confirmed that intrathymic injections of brain antigens can induce immune tolerance by the reeducation function of the thymus.[110] In that study, T cells were isolated from the spleens of C57BL/6 mice after intrathymic injection of MBP in the experimental group. The T cells were cocultured with BV-2 microglia cells in the presence of MBP. Compared with the control group, the CD4+ T/CD8+ T ratio was reduced, CD154 was downregulated, CD152 was upregulated on T cell surfaces, and pro-inflammatory factors (tumor necrosis factor alpha, inducible nitric-oxide synthase, IL-1β) in BV-2 cells were decreased in the experimental group. It demonstrated that intrathymic injection of MBP could suppress the immune reaction that might reduce the secondary immune injury of brain tissue induced by an inflammatory response. Yang *et al*.[29] reported that intrathymic injection of MBP can induce immune tolerance and reduce SBI.

Liver Tolerance

The liver exhibits a distinctive form of immune privilege, termed liver tolerance. Dendritic cells, Kupffer cells, liver sinusoidal endothelial cells, and hepatic stellate cells are among the specialized antigen-presenting cells that present antigens to T cells to participate in T cell apoptosis, anergy, or the differentiation into Treg.[111] Li and Tian[112] reviewed that the liver can serve as a "school"; in that school, the antigen-presenting cells of liver serve as the "teachers" who "educate" circulating immune cell "students" to induce immune tolerance. Since 1969, when Calne *et al*.[113] first discovered that a mismatched MHC (liver) could be tolerated by the host without immunodepressants, inducing graft tolerance has become a pinnacle of pursuit. Therefore, the liver immune system plays an important role in the formation of immune tolerance. Portal venous injection of MBP can induce the formation of immune tolerance, with the potential to reduce the secondary immune attack role for MBP antigen, thereby having the possibility to protect the brain tissue; the Kupffer cells play a key role in this process.[114] Our research showed that brain injury was treated by hepatic portal vein injection of brain antigens.

Although the skin is considered as an organ where immune responses are easily induced, little attention has been given to skin-induced tolerance. Szczepanik M[115] reviewed that ECs exposed to antigen resulted in the induction of suppressor T cells (Ts cells); the inhibitory mechanisms are also much the same, emphasizing the similarities between these two tissues. The fact that Ts cells can be produced by dermatological immunization may have important implications for the design of therapeutic protocols that aimed at regulating the immune response to autoantigens in autoimmune diseases.

Conclusions

The establishment of immune tolerance mechanism for the treatment of brain injury has a high clinical practical value. Different immune tolerance pathways have their own characteristics. The study of some of these pathways has entered the clinical transformation test stage. Since immune tolerance therapy is an important method to treat brain injury, it is necessary to introduce the ways to induce immune tolerance by mucosal tolerance, liver tolerance, thymus tolerance, and skin-induced tolerance. As for how to translate it to clinical work? Which immune tolerance pathways are best for treating brain damage? Our experience is that chronic brain inflammatory diseases can be treated by immune tolerance induced by the skin and mucosa. And for the acute inflammation of brain, liver or thymus pathway is the better choice because of their minimal invasion and 100% drug absorption. As for which way is better – the thymus or the liver? In our latest research, the same dose of single brain antigen and mixed brain antigen was injected into the thymus and liver, respectively. After cross combination, the evaluation of immune tolerance of the four groups showed that the mixed brain antigen plus liver route had the best effect.[29] The problems that need to be solved urgently are that oral immune tolerance requires a large number of antigens, approximately 100 times the dose of antigens used for nasal mucosal immune tolerance; the autologous brain tissue antigen injection pathway is limited by the amount of autologous brain tissue and CSF; the use of allogeneic brain tissue antigens or stem cells presents with infection and/or ethical issues. Therefore, according to the types of diseases and individual differences, the selection of highly

effective drug types and safe administration routes to achieve individualized treatment is the development trend of immune tolerance reconstruction in the future.

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Conflicts of interest

There are no conflicts of interest.

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免疫耐受疗法：创伤性脑损伤治疗的新方法

摘要

目的：由于中枢神经系统特殊的解剖结构和病理生理机制，造成脑损伤后修复与机体其他系统存在较大差异。越来越多的证据表明，针对性的降低脑组织的自身免疫反应，而不影响机体其他部位免疫功能的治疗方法将是治疗脑损伤的最佳优化方案。
数据来源：本文收集了直至2017年6月5日在PubMed数据库内的关于免疫耐受和创伤性脑损伤的相关文章。所有关键词是“免疫耐受”、“创伤性脑损伤”、“中枢神经系统”。
论文选取标准：所有在中枢神经系统中研究免疫耐受和脑损伤的论著及重要的综述均包含在本文研究范围内。我们也对检索到的文献中的参考文献进行了进一步筛选，以尽可能涵盖所有相关文献。
结果：中枢神经系统通过血脑屏障与免疫系统相隔离，在发生脑损伤后，脑抗原释放到全身循环引起损伤性的免疫反应。免疫耐受可有效减轻脑损伤后脑水肿和神经系统炎症反应等症状，有利于神经功能的恢复。创伤性脑损伤的免疫耐受治疗具有较好的临床应用前景和理论研究价值。
结论：免疫耐受机制的建立在创伤性颅脑损伤的治疗中具有较高的临床应用价值，它为患者的脑损伤治疗开辟了新的机遇。