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DEFENCE MECHANISMS OF THE CENTRAL NERVOUS SYSTEM

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SUMMARY

The close relationship between the immune system and the central nervous system (CNS) has been well-studied. The CNS regulates almost all the functions of the immune system; however, the effect and/or the control of the immune system on the CNS has not been well-studied yet. Recent reports suggest that the CNS has its own defence mechanism(s). In this review, attempts have been made to discuss some of the controversial issues in order to approach a clear conclusion.

KEY WORDS: *Central nervous system; Cytokine; Defence mechanisms; Immune response; Immunology.*

INTRODUCTION

The notion that a brain tissue graft is usually accepted and the rejection of the grafted tissue is normally a prolonged process led scientists to believe that the immune response in the central nervous system (CNS) may differ from the other organs (1). There is a striking analogy between the CNS and immune system in terms of function and even anatomy (1,2). The two systems are very similar to each other in terms of diversity. The immune system faces an extremely vast and diverse spectra of antigens to which it must respond in order to eliminate them. The CNS contains an immense number of neurons with a great diversity of the morphological types. Each neuron receives hundreds of synaptic inputs which are stemed from different stimulation processes. Proper responses is sent to the targets in a manner similar to the responses sent by the immune system. Both systems use soluble mediators for communication with the elements of the system and with the other systems such as the endocrine system (3).

The issue of the clonal selection is also common in both systems. Just as the thymic and bone marrow, selection of T and B cell clones has been proposed for the deletion of futile and dangerous clones; selective survivance of neurons was suggested to take place during the embryogenesis of neuron junctions.

Another common characteristic of the two systems is specificity. Immunocompetent cells have the capability to distinguish between very similar peptide determinants. Their recognition is based on the specific engagement of the receptors with their particular ligand. The CNS has also a similar phenomenon .

Both systems possess the ability to store and retrieve the information about the events sensed or experienced by their cells. This phenomenon, which

is referred to as memory, is undoubtedly a sophisticated process with exceptional precision.

Complexity is another common feature of the both systems. The complex networks of lymphokines, antibodies, cell subsets, and receptors lead to the enhancement or suppression of the immune response. The nervous system with its diverse physiological functions and responsiblities in maintaining an acceptable level of control over voluntary and involuntary functions of the body may face an even more challenging level of complexity.

Having mentioned the similarities of the two systems, some major differences should be noted. While immunocytes move about freely, neural cells are fixed in their positions. Cell-cell interactions in the immune system, mostly involve a direct contact of the cells with each other, while nerve cells interact via the elongated processes of neurons and glial cells (1). In the light of the above mentioned similarities, to which others will undoubtedly be added, we wish to study the impact and function of one system on the other.

THE BLOOD BRAIN BARRIER

The central nervous system is regarded as a privileged site with respect to immune function. This is due to the functional and anatomical restriction referred to as the blood brain barrier. This barrier regulates the entry of fluid, electrolytes, proteins, and small molecules from the blood into the extra-vascular space. Neural tissues are surrounded by a fluid which is different from the intercellular fluids. This fluid contains less protein and immunoglobulin (Ig) as compared to plasma (4,5). The barrier consists of a series of regulatory interfaces which determine the entry rate and the quality of substances that pass into the brain. Three surface layers actively participate in this function:

1) epithelium of the chroid plexus;
2) endothelial cells of the cerebral capillaries;
3) layer of cells lining to the arachnoid membrane.

The extracellular fluids of the brain are in three compartments:

1) blood;
2) interstitial fluid;
3) cerebrospinal fluid (CSF).

Hence, the barrier funtions to demarcate these compartments:

1) the barrier between the vascular and brain compartments;
2) the barrier between the vascular and CSF compartments;
3) the barrier between the brain and CSF compartments (6).

The CSF is derived from plasma: 70% is produced by choroid plexus; 18% is stemed from the capillary bed of brain meninges; and 12% is derived from metabolic water production (4). The fluid secreted by the plexus is filtered through the walls of the choroidal capllaries. Proteins are prevented from entering the capillaries. Proteins are also prevented from entering the CSF by the lining of cuboidal cells of the choroidal epithelium. These cells are connected by the tight junctions which form a continuous sheet of epithelium restricting the passage of proteins. In fact, less than 1/200 of protein molecules succeed to pass this barrier (4).

The interstitial fluid is derived from the brain capillaries which have endothelial cells joined by the tight junctions producing a filtrate, low in protein, like the CSF (4,6).

Astrocytes have an important role in the main--tenance of this barrier. Their foot projections, close to the capillary wall, impede the passage of proteins.

The blood brain barrier is incomplete in certain sepcific areas such as the posterior pituitary, the pineal, tuberanereum, areapostrema, and the floor of the fourth ventricle; therefore, porteins can easily penetrate into this area (6). Activated T cells, regardless of their specificity, penetrate into the normal blood brain barrier providing the CNS with a degree of immune surveillance; however, resting T cells appear to be unable to cross the intact barrier (7,8).

Apart from the neurons that have the role of transmitting electrochemical impulses to other cells, the CNS consists of another population of cells which can metabolically support the neurons. The glial cells have an important role in regulating the biochemical milieu of the neurons they form and also sustain the myelin sheath.

Recent studies show that this population of cells may be the immunocompetent cells of the brain.

The glial cells are classified into the following types:
1) oligodendrocytes;
2) astrocytes;
3) microglia cells;
4) radial and peripheral glial cells.

The resident macrophages of the brain are the microglia cells. Studies show that they do not carry the conventional markers, suggesting that they are from a separate lineage. However, they have shown to possess phagocytic activity and carry Fc receptors too. It should be noted that during the injury of the CNS, the most active phagocytic cells are derived from the blood (4).

IMMUNE RESPONSE IN THE CNS

During an inflammatory process, injury or infection, drastic alterations in the blood brain barrier occur. Lymphocytes pass the endothelial cells by emperopdesis and along with macrophages they accumulate in the Virchow-Robin space in the meninges or in the subarachnoid spaces. Recently, the intercellular adhesion molecule (ICAM-1) and its integrin ligand lymphocyte function associated (LFA-1) molecule have been detected on the micro-vessels, glial cells, and mononuclear cells (9). It is speculated that these molecules may play a role in the influx of leukocytes into the CNS and also in the cellular interactions between the parenchymal cells and immunocompetent or inflammatory cells (10).

The effect of the acute inflammatory reaction is to increase the levels of both immunoglobulins and complement in the extravascular space. In the early stages, this may be due to the increased permea--bility. However, as the disease progresses, it may be supplemented by the local antibody production in the CNS (4). The following evidence suggests that local antibody synthesis may occur when:
1) immunocompetent cells are present in the CNS;
2) Ig levels in the CSF are higher than that can be accounted for by the plasma transduction;
3) CSF Igs differ qualitatively from those in the serum.

Studies on the various pathological conditions in the brain report of the excessive antibody production in the CNS. In the diseases such as neurosyphillis, tuberculosis, subacute sclerosing panencephalitis (SSP), and multiple sclerosis (MS) the intrathecal production of the Igs have been observed (4,10). The characteristics of the locally produced antibodies differentiate them from the Igs in the normal CSF which are derived from the serum.

The titer is an important marker since the antibody titer for the certain antigens may be higher in the CSF than serum. Tests have confirmed that at least some of the newly synthesised antibodies in measles, encephalitis and mumps have specificity for the invading organisms (4). In the case of encephalitis caused by *Herpes simplex* or *Varicella zoster viruses,* specfic antibodies have been found that were absent in the serum (12).

The immunoglobulin produced in the CNS has been reported to be associated with the restricted heterogenicity.

In the case of SSP, a discrete and homogenous Ig band, that may fulfill the criteria for monoclonality, is present on the electrophoresis of the CSF. This may be explained by the fact that the number of immunocompetent cells in the CNS is relatively small, and thus the number of clones capable of reacting to a particular antigen is proportionately reduced. Here, the oligoclonal response in the CNS is a consequence of its relative isolation from the lymphoreticular system (4,12). Other reports indicate the production of specific antibody in the brain while it is absent in serum (12).

The next issue concerns the differences in subclasses and kappa and lambda chain ratios. The k/l ratio in the serum is 2/1. In MS, SSP, and chronic meningitis this ratio is elevated in the CSF. Free light chains can also be detected in the CSF during these diseases (4,7).

Recent works have demonstrated the presence of Ig superfamily molecules in the CNS with a possible role in cell-cell adhesion and interaction between neurons and glial cells (13-16). These molecules may have a role in the differentiation of neural cells or they may generate a diversity in neural connections (1).

GRAFTING IN BRAIN

Grafting of histoincompatible tissue in the CNS shows a prolonged but not permanent graft survival (17-19). This means that the immune response and its regulation in the brain are identical to non-privileged sites in the body. The possible mechanisms that cause prolonged graft survival may include:

1) low or lack of MHC expression in brain (5,17,20);
2) low passage of the immune cells across the blood brain barrier (4,18);
3) the brain has a few dendritic cells; therefore, it may result in low antigen presentation ;
4) lack of lymphatic drainage from brain and a probable vascular route for Ag presentation (17);
5) presence of suppressor cells or local immunosuppressive agents (17).

Researchers have noticed that radiolabled tracer substances, injected into the brain, pass into the lymph nodes of the neck. In the rat, 50% of tracers, placed in the forebrain, drain into the lymphatic system while 70-80% drain into the CSF when injection is done in the hindbrain. Certain studies show that the phenomenon of the brain being a privileged site cannot be adequatly explained by the lack of the lymphatic drainage from the brain, at least not in the laboratory animals (17). It is shown that the deep cervical lymph nodes serve as a regional lymphatic tissue in a functional linkage with the brain parenchyma and as an amplification process in the immune response.

There are reports of extracranial metastasis of the primary brain tumors in humans without prior surgery; this metastasis has primarily occurred in the deep cervical lymph nodes (17). Recent works indicate that three perivascular spaces along the major vessels in the human brain serve as a drainage route to the lymphatic tissue. The transition of these spaces resembles a lymphatic tissue in the chronic inflammatory reactions such as MS (7,17).

IMMUNOCOMPETENT CELLS IN THE CNS

Astrocytes may function as antigens (Ags) presenting cells they are known to present Ags in-vitro. Microglia, resident macrophages of the brain, have also been shown to present Ags.

The role of astrocytes, in the brain, is to guide axonal development and to establish hemostatic mechanisms in neutrophils and blood brain barrier and CSF barrier. Astrocytes can also perform the functions of the accessory cells:

a) MHC expression (21,23);
b) Ag presentation (21);
c) release of cytokines (11);
d) the phagocytic and enzymatic activities (21).

Investigators have identified two types of the astrocytes: Type 1 cells are polygonal and constitute the main cells of the adults' CNS. Type 2 cells are processes bearing perinodal astrocytes. Type 1 cells have been used more in in vitro studies, and the factors secreted by type 1 cells can influence type 2 differentiation. In addition to forming gap junctions with ependymal cells and oligodendrocytes, astrocytes have a key role in providing signals for the formation of the tight junctions in the blood brain barrier. It is believed that they allow the selective passage of the antibodies through the blood brain barrier (21).

During an inflammation, neuroligands and astrocytes are stimulated by:

1) cell contacts, involving immunological adhesion molecules like LFA-1 and ICAM-1 (9,21);
2) cytokines released by activated T cells, macrophages and astrocytes (21,22);
3) antigen-antibody complex with or without complement (21).

Brain astrocytes, when activated by lipopoly--saccaride (LPS), produce an interleukin-1 (IL-1) like the factor which shows the same activity as monocyte IL-1 (21,24). LPS treated astrocytes secrete.a substance with suppressor and helper activities. Suppressor activity is possibly due to prostaglandin E_2 (PGE_2). Several lines of evidence indicate that IL-1, produced by the astrocytes of the mouse injected with LPS, may be the major source of the IL-1 in vivo because:

1) astrocytes secrete more IL-1 than macrophages (21,24);
2) many astrocytes are present in the CNS (21);
3) the spleen has low concentration of IL-1.

Astrocytes play a key role in the protection of

the CNS; in case of injury, the repair of the barrier and circuits depends on these cells (21,22). In the initial phase of CNS response to trauma (reactive gliosis), reactive astorcytes become hypertrophied, their mitotic activity and their content of glial fibrillary acidic protein will increase. It is conceivable that various cytokines are involved during these processes (25). Interleukin-1 has been shown to be a potent mitogen for rat's astroglial cells. The release of IL-1 by the inflammatory cells may promote the astroglial response that occurs in the mammalian damaged brain. In a recent study, it has been shown that an astrocytoma cell line can produce various cytokines including IL-6 and IL-8 in response to IL-1 and tumor necrosis factor-alpha (TNF-alpha) (25).

Interleukin-1 may have a role in the neuronal repair following injury since it has been observed that IL-1 stimulates the production of nerve growth factor and its receptor after sciatic and splenic nerve lesions (26).

In glioblastoma, cell lines production of IL-6 is regulated at the transcriptional level by a nuclear binding factor NF IL-6. Interleukin-6 is produced by astrocytes, T lymphocytes, macrophages, and microglial in response to viruses to IL-1, TNF, or LPS. It promotes the differentiation and production of cytokines in a wide variety of cells. It enhances infectious or inflammatory processes in which it participates (21).

Cytokine production has also been induced in human fetal microglia and astrocytes but stimuli for the induction differs. Lipopolysaccaride is a potent stimulus for microglia while astrocytes respond primarily to IL-1ß. Microglia is considered to be the key regulator of astrocyte response through the expression of IL-1ß (27). Proliferation and swelling of astrocytes in the CNS have been observed in the experimental autoimmune encephalitis (EAE) and MS. In MS patients, there is also an increase in lysosomal enzymes. Stimulated astrocytes release enzymes and mediators such as: C_3, ß, arachidonates, PGE_2, thromboxane, and leukotriens (8,21,28). Astrocytes may be the targets for CTL; and, tissue specific MHC expression plays a role in the regulation of the immune reactivity.

ANTIGEN PRESENTATION IN THE CNS

In the recent years, studies have indicated that these molecules which play a central role in immune responses are not detectable in resting neurons, oligodendroglia, and astrocytes. The lack of MHC expression has been attributed to the absence of positive regulation or the presence of negative regulatory mechanisms. Research on the regulation and control of the experssion of MHC genes is in progress (21).

Cultured murine cerebral vascular endothelial cells stimulated with interferon gamma (INF-gamma) express MHC class II and can present Ag (MBP) to T cells. Rat's brain endothelial cells, when stimulated, express class II but are not as effective as antigen presenting cells (APC) for MPB or tuberculine. This is due to lack of co-stimulatory signal. However, ICAM-1 and LFA-3 have been demonstrated on cerebral vascular endothelium (21). $CD\text{-}4^+$ and cytotoxic T lymphocytes (CTL) have been shown to lyse activated MHC class II positive endothelium in the presence of MBP. This lysis in EAE or MS manifests vascular damage and facilitated entry of the inflammatory cells to the brain parenchyma (7,28). Other research on MHC antigens in the CNS indicates that the CD-4 molecule is present in the brain; however, the size of the CD-4 mRNA in the brain tissue is smaller than the immune system, suggesting that a differrent subtype of the CD-4 molecule is present in the brain (29-31).

Cultured human astrocytes respond to INF-gamma by the increased experssion of both classes of MHC and ICAM-1. Interleukin-1, TNF, and INF-gamma stimulate proliferation of the astrocytes but not in cells expressing MHC molecules. Interferon-gamma primes astrocytes to respond to IL-1 or LPS by the production of TNF, IL-1, IL-3, IL-6, and lymphotoxin (24). Major histocompatibility complex and ICAM-1 are expressed on astrocytes on the advancing edges of MS plaques and endothelial and inflammatory cells (21).

Researchers have shown that, after certain antigenic challenges, there is an increase in the firing rates of some hypothalamic neurons (23). It

has also been shown that alpha-interferon may increase the firing rate of cortical and hippocampal neurons (33).

Systemic administration of lymphokines into the third cerebral ventricle produces marked behavioral and electroencephalographic (EEG) changes. Other studies have shown that IL-2, injected into the third ventricle of rats, produces a marked increase in the neuronal activity in the supraoptic and para-ventricular nuclei which secrete anti-diuretic hormone. This may explain the water retention observed in patients during IL-2 therapy against cancer (34).

Interleukin-2 activates T cells which specifically trigger the proliferation of oligodendrocytes. Interleukin-2 also regulates the expression of MBP (34). When IL-2 is applied through the cannulae to several areas of the brain, it is able to effect on the gross behavior (34). Dose dependent soporific effects and increases in the EEG spectrum power have been observed. Interleukin-2 produces sleep, promoting effects mediated through the locus coerules. The inhibition of the cell firing by IL-2 might explain the soporific effects observed during IL-2 treatment in cancerous patients. The electro-physiological and behavioral effects of IL-2 seem to be due to the activation of specific receptors (34).

These data indicate that lymphokines may involve in the control of specific functions in the CNS under physiological conditions.

The pathological conditions, excessive sleepiness, and fever during the infectious diseases may be related to the endogenous release of lymphokines which may play a role in safeguarding, repair, and hemostatic mechanisms in response to trauma in the CNS. The effects observed following the injection of IL-2 in the specific areas of the brain proved that IL-2 receptors may exist in neurons. Data, presented on this matter, indicated that the central effect of IL-2 is due to the stimulation of the specific receptors probably coupled through a Gi-protein to adenylate cyclase (34). Other researchers have questioned whether the IL-2 receptors found in the brain are identical to that of the immune system (35). Interleukin-2 has been used in cancer therapy, however with troublesome CNS side effects.

It has been shown that when IL-1 and IL-2 are injected systemically, they can reach areas of the CNS where the blood brain barrier is absent or becomes permeable by the pathological conditions. Messenger-RNA for IL-1, IL-2, and IL3 has been localized in the discrete areas of a mouse brain both in neuronal cells and astrocytes. In rat, the highest concentration for IL-2 binding sites is in the hippocampus (35).

Some researchers have found a role for TNF-alpha in the CNS (36). Although it is not clear whether TNF-alpha is produced locally,it has been shown to increase the circulating catecholamines and cortisol and selectively stimulate ACTH secretion, the former in dog's and the latter in rat's CNS. It has also been shown that microglial cells are able to perform TNF-alpha medicated killing cells (36).

It has been suggested that cytokines regulate pituitary hormone secretion via the brain and hypothalamus (37). Specifically, it has been shown that the tumor necrosis factor induces the release of beta-endorphin and the growth hormone from the rat's primary pituitary cell cultures (36).

IMMUNOPATHOLOGY

Two pathological conditions which may serve as models providing insight into the immunological mechanisms in the CNS and neuroimmune interactions are primary intracranial tumors (gliomas), and MS (a demyelinating disease with autoimmune etiology).

Gliomas are tumors of the glial cells, which grow in any site of the CNS, resulting in the progressive neurologic dysfunction. They have been associated with impaired host defence system, featuring T cell lymphopenia and impaired T cell responsiveness to different stimuli (38). The production of IL-2 and the expression of the p55 chain of the IL-2 receptor is compromised in these patients. Sera of the patients have also been shown to exhibit suppressive activity on lymphocytes and a glioma derived suppressive factor, known as G-TSF, has been isolated and characterised (39,40).

Multiple sclerosis is a demyelinating disease of the CNS in which both cellular and humoral mechanisms have been impaired. The sequence of

events is usually defined as follows:

1) multifocal infiltration by perivascular inflammatory cells ;
2)macrophage mediated myelin degradation ;
3)reactive astrocytosis and oligodendrocyte depletion (18,28).

Experimental and clinical studies have led to various hypotheses in this regard. Two major theories on the etiology of MS exist: The first proposes that the inflammatory response in the brain is an anti-viral immune response. The second suggest that MS may be an autoimmune disease caused by infiltrating T cells, recognising self-antigens (18).

Most studies led to the suggestion that the development of a demyelinating lesion requires two events: cell mediated damage to the blood brain barrier which then permits the entry of macrophages and soluble mediators necessary for their physical attachment to the oligodendrocytes and myelin (7).

According to this theory, antibody independent complement activation by oligodendrocytes results in the appearance of macrophages and local antibodies which lead to demyelination (7).

Other researchers believe that autoreactive T cells actually play the central role in the pathogenesis of MS. They propose that since resting T cells cannot cross the blood brain barrier, myelin basic protein (MBP) reactive T cells have to be activated in the periphery to infiltrate the CNS white matter and to initiate an inflammatory response. Possible mechanisms for the activation of MBP reactive T cells in the periphery in the absence of MBP include: superantigens molecular mimicry and T cell activation (8).

FUTURE DIRECTIONS

The immunology of the nervous system is a relatively young field as compared to other areas of immunology or neurology. Considering the intrinsic similarities between the two systems, it could be speculated that progress in one field will inevitably influence viewpoints and postulates the other.

Future research on the immunology of the CNS will require a thorough study of accessory molecules and co-stimulatory signals on the glial and neural cells, the biochemical interactions involved in signal transduction, the molecular mechanisms of tolerance, and cytokine networks.

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