Neuroimmunomodulation Countering Various Diseases, Disorders, Infections, Stress and Aging

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ABSTRACT

Neuroimmunomodulation involves interactions among nervous, endocrine and immune systems. An integrated function is performed by nervous and immune systems that is responsible for preservation of integrity and homeostasis of the organism. Though Central Nervous System (CNS) has a limited repertoire for its own protection, it has the Blood Brain Barrier (BBB) and the capacity to engage peripheral immune system to eliminate infections and xenobiotics. Neural cells involved in the process of providing neural immunity include: Glial cells, astrocytes and oligodendrocytes. Besides working as sentinels to get rid of pathogens in the process of neurodevelopment, both central as well as peripheral immune cells actively participate helping in cognitive brain functions. Neurogenesis process may also be regulated by adaptive immune cells peripherally. Recently there is a discovery of cholinergic anti-inflammatory pathway wherein vagal nerve has shown anti-inflammatory role in endotoxemia and shock. Hormones viz., nor-epinephrine, epinephrine and glucocorticoids prepare immune system to combat infections and enhance distribution and trafficking of immune cells by several ways. This review focuses on neurobiology, neuro-immune cross talk, neuroimmunoregulation, stress and neuroimmunomodulation which will be beneficial for researchers, professionals and academicians. Topics like neurotoxic and neuroprotective roles of immune reactions (which are innate in nature) in the process of aging are highly debated among researchers. In this review, topics like neuroinflammation and neurodegeneration, role of vitamins, minerals, herbs and drugs and volatile oils in the process of neuroimmunomodulation and particularly counteracting various diseases, disorders, infections, stress and aging have been discussed vividly to enhance and update the knowledge of the scientific community regarding this particular topic 'Neuroimmunomodulation'.

Key words: Neuroimmunomodulation, neural immunity, diseases, disorders, infections, stress, aging, neuroimmune cross talk, neuronal cellular interactions, neuroimmunomodulators, vitamins, minerals, herbs, drugs, neuroinflammation, neurodegeneration, neuroimmunoregulation, health
INTRODUCTION

Both the nervous system as well as the immune system act in coordination. It is more appropriate to say that complimentary functions are performed by the nervous as well as immune systems which contribute to preservation of the integrity as well as homeostasis of the organism. A compact cell networks form these two systems which help in monitoring and processing, along with creating response to changes in external as well as internal environment that include extracellular tissue spaces. The two systems work in concert which is evident from their similar functions and use of common receptors, ligands along with other communication molecules (cell-to-cell). It is interesting to observe that there has been exponential growth of knowledge on the immune response to neuronal functions. At the barrier regions viz., skin, lung and gut, mast cells and eosinophils interact with pathogens thereby forming the main frontier of neuroimmune cross talk. In case of infectious diseases common manifestations are behavioral changes that reflect changes in mood as well as motor activity. Many studies have reported the influence of depression and other psychological disorders on reactions of the immune system. A rapidly growing field of molecular as well as cellular neuroscience has evidently shown the interaction (bilateral) of nervous and immune systems (Blalock, 2005). Several of the immunomodulatory regimens are present in plants, herbs, fruits, vegetables, vitamins, minerals and apart from these novel and emerging immunomodulatory substances include probiotics, cytokines, toll like receptors, drugs and others (Mahima et al., 2012, 2013, Dhama et al., 2008, 2013a-c, 2014; Rahal et al., 2014a).

Neuroimmunomodulation involves the interactions among the nervous, endocrine and immune systems. The nervous system influences the immune system via neural and hormonal actions (Spector, 1990). It is established for many years that immune system is innervated by nerve endings but their functions on those organs are not fully known and needs full elucidation. Earlier the immune system was believed to be functional independent of the nervous system in the body. However, about 30 years back knowledge started emerging that the Central Nervous System (CNS) could be involved during immune responses and any defect in the CNS circuit results in autoimmune disorders. This has given way to the new concept of immunomodulation that nervous system recognizes the endocrine and immune systems and their interactions changed the course of immune system. Currently it is one of the rapidly expanding and exciting fields in biomedical science (Chambers and Schauenstein, 2000). Immune system sends and shares signals with the nervous system and cross talk between the three physiological systems namely immune, endocrine and nervous system are carried out by various cytokines, neurotransmitters, neurosteroids, neuropeptides, cyclic nucleotides and calcium and protein kinases. They function as mediators between nervous and endocrine systems and also can mediate actions within the system. Their functions differ depending on location, so the signaling molecules of neuroimmune dialogue can be reclassified when sufficient evidence for neuroimmunomodulation accumulates (McAllister and Van de Water, 2009). Brain is protected mechanically by skull bones and biochemically by various barriers. Immune cells are not the exception, so the nervous tissue is clearly and selectively secluded from the peripheral immune cells. At the same time, any small inflammation and immune reaction will cause loss of CNS function. So the immune system follows a different set of parade to protect the nervous system from the pathogens and this process is also modulated by nervous system. Exaggerated immune responses are involved in the pathogenesis of several degenerative disorders. At the same time, absence of immune stimuli also produces development disorders of CNS. So this review is focused to delineate the neuroimmunomodulation with respect to the neural immunity and neural degeneration. It discusses neuroimmunomodulation and its various beneficial health aspects, nervous system and neural immunity, immune cells and their functions, neurobiology of cells, neuroimmune cross talk and neuronal cellular interactions, neuroimmunoregulation, neuroinflammation and neurodegeneration and particularly various neuroimmunomodulators counteracting diseases, disorders, infections, stresses and aging with special focus on vitamins, minerals, herbs, drugs and others.

NEURAL IMMUNITY

Immune dysfunction usually affects the course of CNS diseases caused by microbes or trauma; toxic metabolite; autoimmunity; or partly due to a wide range of degenerative processes. Multiple disciplines including but not restricted to molecular neuroscience; neuroimmunology; virology; immunology (cellular); receptor pharmacology; neuronal electrophysiology; neurochemistry; neurology (clinical); as well as developmental neurobiology have been involved in study of immune system dysfunction and its relation with homeostasis. Such studies are based on the hypothesis that mononuclear phagocytes in brain (viz., perivascular as well as brain macrophages along with microglia) act as disease inducers by engagement of the immune system for protecting, defending or inducing neural injury. It is indeed the macrophages in the brain that act as scavengers that kill microbial pathogens, cause regulation of immune response through presentation of antigen; as well as mobilizing adaptive immune responses. Thereby, they affect the production of neurotrophic or toxic secretory factors that incite the process of disease. It is however, important to note that therapeutic modalities may be advantageous as far as the immune responses in the CNS are concerned via vaccination thereby leading to generation of neuroprotection (Gendelman, 2002).

Though CNS has a limited repertoire for its own protection, it has the Blood Brain Barrier (BBB) and the capacity to engage peripheral immune system to eliminate infections and xenobiotics. It has its own innate immunoregulatory cells comprising of glial cells,
oligodendrocytes and endothelial cells. These cells involved in development and protection of the brain (Gendelman, 2002). Immune responses are regulated by cytokines perhaps through activating Hypothalamic-Pituitary-Adrenal (HPA) axis. More and more auto-immune T-cells are involved in the process of neurogenesis. It has been found through several research works that adaptive immune responses increase neurogenesis in the hippocampus. It is a proven fact that T-cells as well as microglia are important for the process of neurogenesis (Ziv et al., 2006, Bessis et al., 2007).

It must be remembered that pro-inflammatory cytokines are the molecules that can affect growth of the brain along with function of the neuronal system. Such cytokines are interleukin (IL)-2, IL-6, IL-12, interferon (IFN)-gamma and Tumor Necrosis Factor alpha (TNFα). Such molecules are secreted by circulating immune cells such as microglia and astrocytes (Papanicolaou et al., 1998; Covelli et al., 2005).

INVOLVEMENT OF NEURAL CELLS

Glia: An exceptional feature in the adult brain is adult neurogenesis which helps to form a bridge between neuronal as well as glial neurobiology (Morrens et al., 2012). All classes of glial cells are involved in adult neurogenesis. In the adult brain, radial glial like cells with astrocytic features, present in hippocampal dentate gyrus and the subventricular zone of the lateral ventricles, produce new neurons and are themselves produced to create microenvironment for the process of neurogenesis (Morrens et al., 2012). Further, certain precursor cells generate oligodendrocytes which are intermingled with other neuron generating cells in an independent lineage (Morrens et al., 2012). In the brain of adult mammals the most frequent cell types are astroglia that show a broad range of diversified functions. One of the most striking feature is their function as neural stem cells (adult) thereby contributing towards the process of neurogenesis. There are various features shared by radial glial cells with neuroepithelial cells which gave the name “radial glia”. In the mammalian brain at the end of the process of neurogenesis there is disappearance of radial glial cells and there is transformation of a subset of these cells into astroglial cells. It is interesting to note that certain astrocytes are helpful for the maintenance of neurogenic potential which helps in continuing the generation of neurons throughout the entire life (Mori et al., 2005).

Glia cells can be largely divided into microglia and macroglia. The former one is equivalent to the macrophage of the peripheral immune system and latter is otherwise called as astrocyte. Both cells protect the CNS from degenerating inflammatory responses. Microglia, the resident immune cell of the Central Nervous System (CNS), plays an important role in CNS homeostasis during development, adulthood and ageing. Origin of the microglia and its naming as CNS macrophage is still a topic of debate for many scientists. Microglia are said to be derived from yolk sac during development but in adult CNS, many of non-yolk sac populations are also present; contribution of bone marrow for microglia population is largely unknown. The microglial cells are different from the macrophages as they are long living, slowly proliferating and self-renewing population of immune cells and they are present only inside the brain. Their main function is the synaptic plasticity (pruning extra synapses and phagocytosing post synaptic neurons) thereby limiting the number of synapses in CNS. They are the cells responsible for the normal development of CNS. But they are the principal foe for the nervous degeneration in case of inflammation. Microglia function is tightly regulated by the microenvironment in the CNS and several evidences suggest that neurodegeneration, ageing and other neural insults, can influence the microglial phenotype and function. Several neurotrophic factors like nerve growth factor, brain-derived neurotrophic factor dampen the immune response of the microglial cells. They also express receptors for gama-aminobutyric acid (GABA) and noradrenaline (NE) to have immunomodulatory effects on them. Their location is limited to brain and but distributed unequally. They circulate all over the brain and survey the neuronal functions. Meningeal and perivascular macrophages are derived from blood compartments as they are actively involved in phagocytosing pathogens entering brain via blood. Microglial cells can interact with these macrophages and chemokines of the peripheral origin and they can alert the nervous system for the immune responses (Perry and Teeling, 2013). Resting microglia express the MHC class II molecules but once get activated it will become amoeboid cells and expresses a variety of receptors such as chemokine/cytokine receptors, Toll Like Receptor (TLR), mannose receptor, opioid receptors, cannabinoid receptors, benzodiazepine receptors, complement receptors, purinergic receptors, integrin receptors, cell adhesion molecules receptor, immunoglobulin receptors etc., to recognize various stimuli of peripheral nervous system. They also secrete several interleukin types, TNFα, TGFβ, various chemokines, matrix metalloproteinases (MMP), eicosanoids, cathepsins, complements, nerve growth factor, fibroblast growth factor, glutamate, Amyloid Precursor Protein (APP) and free radicals. Receptors and secretory products are involved in nerve defense mechanisms and in excess they cause damage to the neurons (Rock et al., 2004).

Astrocytes: Early microscopists called these cells as macroglia, the term glia (glue/sludge in Greek) is contemptible since these cells are highly fibrous and complex structures and have many fine processes that are in contact with thousands of neuronal synapses (Nedergaard et al., 2003). On the other hand these processes surround the vascular cells to form perivascular foot processes of blood brain barrier. They are thought to be a mediator for neuro-vascular coupling because of their strategic positioning between brain capillaries and neuronal synapses. This hypothesis is confirmed by discovery of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex forming proteins and presence of purinergic and glutamnergic transmission. The
basic functions of the astrocytes are to provide optimum environment for the neuronal function. Astrocyte membranes express ion channels such as inward potassium rectifier (K$_{ir}$), big conductance Ca sensitive potassium channels (BKCa) and glutamate channels, they are involved in shaping of neuronal output and controlling neuronal inhibition. They are interconnected by gap junctions made by proteins called connexin-43 and connexin-30; this allows free flow of glucose from blood vessels to many astrocytes and provides nutritional supply to the neurons (Halassa and Haydon, 2010). Astrocytes are also involved in clearing of metabolic end products and act as signaling molecules for neurotransmission. They respond to Ca$^{2+}$ spilt out after the synaptic activity, this will cause raise of Ca$^{2+}$ in the astrocytes, this suppresses the neuronal excitability (Nedergaard et al., 2003). When the astrocyte functions are impaired during ischemia of brain or due to other insults this may influence critically the survival of neurons. Functions of astrocytes that use to help in survival of neurons include: uptake of glutamate and their release; scavenging of free radicals; transport of water and cytokine and nitric oxide production. Expression of astrocyte surface molecule and release of trophic factors influence the recovery (long-term) of injured brain through outgrowth of neurite; plasticity of synapses; or regeneration of neurons. Additionally, the ultimate clinical outcome may be affected by the death or survival of astrocytes themselves. Rehabilitation thereby occurs through influence on neurogenesis and reorganization of synapses (Chen and Swanson, 2003). Their role in innate immunity is less important than microglia but they actively participate in adaptive immnunity. Astrocytes secrete chemokines, express several receptors like Complement Receptors (CR), Pattern Recognition Receptors (PRR) e.g., Toll Like Receptors (TLR), scavenger and mannose receptors) and co-stimulatory molecules involved in the antigen presentation. They interact with neutrophils of blood and reduce their activity. Astrocytes downregulate the activation of monocytes and microglial cells to reduce neuroinflammation (Tian et al., 2012). In brief, astrocytes are supporting cells of the nerves; they nurture the neurons, respond to external stimuli and control the synaptic transmission and have limited role in neural immunity compared to the microglia. A neuroprotective role during inflammation of brain is played by glutamate which is uptaken by astrocytes. Primary fetal astrocyte culture of human origin has been used for investigating the influence of particular cytokines on the activity of glutamate uptake. Tumor necrosis factor-alpha and IL-1β inhibit glutamate uptake by astrocytes whereas interferon-gamma does opposite. IL-1β mediated glutamate uptake inhibition is facilitated due to the blockage of the nitric oxide synthase inhibitor (NOS-monomethyl-L-arginine). This suggests the nitric oxide involvement on IL-1β effect. The inhibitory effects of cytokines have been reversed by IL-1 receptor protein antagonist. The process of generation of nitric oxide is reduced which is corresponding to the anti-inflammatory cytokine IFN-beta blocked cytokine. These findings when taken together suggest that there is an inhibition of astrocyte glutamate uptake by pro-inflammatory cytokines by a mechanism that involves nitric oxide. A therapeutically beneficial effect may be exerted by blockade of nitric oxide production (which is induced by cytokine) in the brain inflammatory disease (Hu et al., 2000).

During the process of ischemia and reperfusion, the primary mediators of neuronal death are glutamate excitotoxicity, oxidative stress and acidosis. In various ways astrocytes influence such processes. In the extracellular space of the brain, prevention of excitotoxic glutamate elevators appears to be a crucial determinant of survival of neurons in the penumbra which is ischemic in nature. Conversely, there may be efflux of glutamate from astrocytes by glutamate uptake reversal; organic ion channels (volume sensitive) and certain other routes may also contribute to glutamate elevation extracellularly. Glycine and D-serine in association with glutamate in reality modulate the activation of N-Methyl-D-Aspartate (NMDA) receptors. Such neuromodulators (both glycine and D-serine) are transported by astrocytes. Neuronal antioxidant status is influenced by astrocytes via release of ascorbate and uptake of its oxidative form, dehydroascorbate. Most probably, these cells also help in survival of neurons in the post-ischemic period too. Several angiogenic and neurogenic factors are also released by astrocytes along with erythropoietin to prevent vascular and neuronal regeneration along with prevention of programmed cell death (Swanson et al., 2004).

**Oligodendrocytes:** The myelinating cells of the central nervous system, form insulating sheath around axons, express monocarboxylate transporter 1 (MCT1) to metabolically support neurons. They help in fast conduction of action potentials and maintaining long-term axonal integrity. They are not directly involved in the neural immunity but their function is to provide nutrients and protect the axonal membrane. Various inflammatory mediators secreted by microglia and peripheral immune system activate the phagocytic cells against nerve cells and myelin sheath resulting in demyelination. This is the basic underlying cause for the multiple sclerosis in human (Lee et al., 2012). The role of oxidative stress has also been proposed for the death of oligodendroglial cells. It is important to note that sphingomyelins-acetamide pathway (neutral in nature) plays a crucial role in oxidative stress-mediated apoptosis. Several agents induce oxidative stress and one such agent is superoxide radical which is produced by hypoxantnine and xanthine oxidase; hydrogen peroxide; inhibition of catalase caused by aminotriazole along with increased level of hydrogen per oxide intracellularly. Neutral sphingomyelins activities are induced due to the effect of reduced glutathione-depleting diamide (Jana and Pahan, 2007). The progression of a disease in the nervous system is also controlled by oligodendrocytes (Kang et al., 2013).

In the central nervous system, emergence of reciprocal signaling occurs between immunocompetent cells that
under-prints pathological as well as chronic pain mechanisms. Strong enhancement of neuronal excitability is possible both by classical neuron derived neurotransmitters along with microglia, astrocyte and infiltrating T cell stimulated-immune mediators (Grace et al., 2014).

In healthy individuals, autoreactive T cells do not cause induction of any overt disease because of their lack of exposure to autoantigen or due to control of the immune system. Activation of protein specific myelin T cells leads to disease induction. Studies with memory CD45RO(+) or naive CD45RA(+) T-cell were carried out in vitro. MOG-reactive T-cells were isolated from most cases under study which was unusual. Compared to IL-4 gamma, interferon was generated in more concentration along with nerve growth factor expression. Such studies have demonstrated that in certain patients there have been activation of MOG-reactive T-cells substantially (in vivo) without evidence of the resultant clinical disease (Burns et al., 2002).

FUNCTIONS OF NEUROIMMUNE CELLS

Besides working as sentinels to get rid of pathogens in the process of neurodevelopment, both central as well as peripheral immune cells actively participate in cognitive brain functions. The process of neurogenesis may also be regulated by adaptive immune cells peripherally. Reduction in neurogenesis and impairment in learning and memory occur due to adaptive immunity deficiency or severe combined immunodeficiency (SCID) or recombination activating gene (RAG-1 (-/-)). Depletion of CD4+T-cells systemically results in significant decrease in neurogenesis in the hippocampus. It has become evident experimentally that neural precursor cell proliferation gradually increases with repopulation of RAG-2 (-/-) mice with CD4+T-cells. It has been found recently that immune activity has been found in association with hypothalamus-dependent stress axis programming. There has been increase in the motor activity in germ-free mice with ill-balanced immune system and subsequently there is reduction in anxiety in comparison to those mice which have got normal microbiota in gut. Transfer of T-cells to RAG-1 (-/-) mice helps in restoring elevation of blood pressure in lieu of stress response (Ziv and Schwartz, 2008; Marvar et al., 2012).

NEURONAL CELLULAR INTERACTIONS

A complex orchestration of the developmental events is essential for nervous system wiring. Transient T-cell-cell interactions in most of the instances serve the purpose of positional cues for guidance of axon as well as synaptogenesis during the process of assembling the neural circuits. Such transient interactions involve cells in contrast to the cellular interactions that are relatively stable between matured synaptic partners in circuits (Chao et al., 2009).

The best understood cellular-extracellular matrix (ECM) interaction is adhesion which is mediated by specific cell surface molecule binding with cell binding domains of ECM components. Adhesion of cell-substratum is necessary for majority of the cell movements during neuron morphogenesis. This is nothing but neural cell migration along with their precursors to facilitate the behavior (migratory) of growth cones at the extending tips of axons as well as dendrites. During the movement of the cells, there is binding of ligands to the adhesive molecules at the leading edge surface of a migrating cell. Filopodia as well as lamellipodia are stabilized by these bonds and in certain instances provision of anchorage against the filaments (cytoskeletal) is done for pulling the cell or growth cone forward. For this reason the ECM is thought to act as an adhesive substratum for providing traction for migrating cells and for stabilization of the position and probably also stabilize the differentiation state of non-motile cells. It has however, been noted that the neural cells and ECM interaction are no longer considered as solely adhesive or mechanical (Strittmatter and Fishman, 1991; Dansky and Werb, 1992; Letourneau et al., 1994).

The activation of the microglia is prevented by neuronal membrane glycoproteins viz., Cluster of Differentiation (CD) 22 and CD47, CD200 and Neural Cell Adhesion Molecule (NCAM) through respective counter-receptor interaction. In neurons, there is expression of immunoglobulin superfamily (IgSF) member CD200. The CD200R (receptor) is an IgSF molecule which is expressed by the cells of the myeloid lineage predominantly that include microglia as well as T-cells. In mice, knocking out CD200R leads to an exaggerated clinical course of Experimental Autoimmune Encephalomyelitis (EA.E). This is in coordination with macrophages’ and T-cells filtration at increased level. In vitro, blockage of CD200R on macrophages leads to enhancement of IL-6 release which is induced by IFN-gamma along with death of neuronal cells in co-cultures with hippocampus neurons that express CD200 (Hoek et al., 2000; Meuth et al., 2008).

CD22 is another IgSF and sialic acid binding molecule whose implication is observed in the attenuation of the CNS immune responses. Cultured cortical neurons express CD22 thereby mediating the neuron binding to microglia via CD45. Microglial CD45 has been ligated by CD22 thereby preventing the LPS induced microglial production of TNF-alpha (pro-inflammatory cytokine). CD47 is a protein found in association with integrin that has been found to be important in down regulation of CNS immune responses. CD47 acts as a cellular ligand for signal regulatory protein-alpha (Tan et al., 2000; Mott et al., 2004).

In vitro studies have shown that glial cells cause inhibition of neurons thereby inhibiting the production of LPS stimulated nitric oxide TNF-alpha. Partial mediation of such effect is done through the IgSF adhesion molecule NCAM. Microglial cells start secreting neuroprotective agents when induced by chronic stimulation as well as interaction with apoptotic neuron. The phagocytosis of apoptotic neurons is also done by triggering receptor expressed in myeloid cells (TREM)-2 receptor while there is a decrease in pro-inflammatory responses of the microglia but no identification of the neuronal ligand has been done yet (Chang et al., 2000; Takahashi et al., 2005).
NERVES TO FIGHT INFECTIONS

Immune system protects the host from all the antigens. In the same way, the nervous system adapts the body to ever-changing external environment. Both the systems perform similar action but in their own way. They converge through various signaling molecules and execute several coordinated essential responses to stress. Both are having threshold for their activation and once activated, the communication is extremely rapid. Nervous and immune systems are intercommunicated and overlapping occurs at various stages (Kawli et al., 2010).

Stress represents a real or seeming perturbation to physiological homeostasis or psychological well-being of anybody. In response to stress, the body uses a constellation of behavioral or physiological modes to combat the perturbation and come back to normalcy (Committee on Recognition and Alleviation of Distress in Laboratory Animals). Stress causes alterations in many organ system functions and prepares the body for fight-flight mechanism. A life cannot exist in an environment without a stress and effect of stress on immune system greatly affects the physiology of an organism. Body senses the stressor stimuli and signals the response to effector organs through nervous system. Hypothalmo-hippocampal-adrenal axis is the intercommunicator between nervous and immune system and actively participates in stress response. It mainly involves sympathetic nervous system and their hormones such as norepinephrine, epinephrine and glucocorticoids. These hormones prepare the immune system to combat infections and enhance the distribution and trafficking of immune cells by several ways. The final outcome would be immunoprotection or immune suppression or immunopathology (Dhabhar, 2009). Normally, glucocorticoids activate the acute immune response and inhibit the chronic cell mediated immune response. So in acute infection it increases pro-inflammatory response both in central and peripheral immune system and they are responsible for the sickness and fever response in animals to maximize the ability to overcome infections (Frank et al., 2013). Studies with Caenorhabditis elegans showed that the integrity of nerves was very important for the dermal and intestinal immunity and resistance to the pathogens. It also confirmed that nerves communicate with the immune system through various transmitters like acetyl choline (ACH), noradrenaline/adrenaline, dopamine, GABA, glutamate and neuropeptide Y (NPY) to modulate the immune response (Kawli et al., 2010). Nervous system responds in a little different way when it comes for own system inflammation. This can be explained by post stroke immunosuppression. In stroke, the nervous system suppresses the immune system by activating stroke activated hepatic invariant natural killer T-cells (iNKT) to protect the brain cells from the life threatening inflammation but that makes the peripheral immune system incapable to fight infection which is the major cause of stroke induced death (Wong et al., 2011). So nerves are required for mounting an immune response in an effective and controlled manner and the final outcome will be clearance of infections without potential threat to the host.

Own nervous tissues are attacked by the body by activation of cells (having receptors for both virus as well as nerve proteins) that fight diseases in case of a virus infection. Triggering of nerve damage is evident by dual-receptor in case of multiple sclerosis. Depending upon the nerves affected, the multiple sclerosis may cause blindness or paralysis. Susceptibility to multiple sclerosis is altered by various viruses that depends on the predisposing genes, exposure to environmental factors, along with a random chance that there have been formation of white cells for recognizing both a nerve protein as well as a pathogen (Li et al., 2010).

CHOLINERGIC ANTI-INFLAMMATORY PATHWAYS

Cholinergic anti-inflammatory pathway has demonstrated anti-inflammatory action of vagal nerve in endotoxemia and shock in recent studies. Neuronal and humoral are the two unique mechanisms in the immune-brain communication. Cytokines, released by dendritic cells, can directly activate the vagal nerve afferent fibers along with immune cells which are associated with macrophages or indirectly through chemo-sensitive cells. Vagal cholinergic pathway has got a special significance in controlling moderate inflammatory reactions. Cytokines in the blood that crosses the Blood Brain Barrier (BBB) can mediate the solitary tract nucleus (NTS) humoral mechanism. One of the penetration sites is area postrema which is found very close to NTS and therefore the cytokines that enter brain can cause activation of NTS neurons. Cytokines can also get bound to the capillary endothelial cell cytokine receptors thereby enhancing the release of various neurotransmitters like nitric oxide (Bianchi et al., 1995; Mauer et al., 1998; Pavlov et al., 2003). Acetylcholine produces direct influence on immune cells. It has been observed that there is expression of nicotinic acetylcholine receptor proteins and synthesis of acetylcholine by the immune cells (Hunyady et al., 1997). In vitro acetylcholine is immunosuppressive in nature thereby leading to decreased levels of interleukins and tumor necrosis factors. Vagotomy cause increased immune reaction that suggests the importance of vagal tone for maintenance of immune homeostasis. Vagal stimulation leads to anti-inflammatory actions in local inflammation models (viz., inflammation in rodents induced by carrageenan) (Tracey, 2002) and such immunomodulatory effect is much rapid than humoral regulation.

NEUROIMMUNOMODULATION AGAINST OTHER DISEASES AND DISORDERS

Both immune as well as inflammatory responses are mediated by cytokines. Maintenance of homeostasis of the body lies in complex interactions between cytokines,
inflammation as well as adaptive responses. Systemic inflammatory reactions cause stimulation of four major programs, these are: The acute phase proteins; sickness behavior; the pain program as well as the stress response. HPA axis along with the Sympathetic Nervous System (SNS) mediates such phenomenon (Miller et al., 2007a). Cytokine processes occur in certain diseases like bipolar disease; depression and mania. The major neurotransmitters in the brain are serotonin, nor-epinephrine and dopamine (or other receptors), the effects of which are reduced during the chronic disease processes mainly due of secretion of glucocorticoids. This further causes neurohormonal dysregulation. There is release of nor-epinephrine into the target organ from sympathetic nerve terminals under stimulation thereby causing expression of adrenoceptors by the target immune cells. There is modulation of cytokine production along with the various lymphoid cells functional actions through such receptor stimulation, releasing nor-epinephrine locally or epinephrine in the circulation. Release of corticotropin releasing hormone (from the hypothalamus) and adrenocorticotropic hormone (from the pituitary) are also inhibited by glucocorticoids (Zorrilla et al., 2001; Boulanger and Shatz, 2004; Szele et al. and Vizi, 2007).

The well-being of the individuals is hampered by such abnormalities due to failure of the adaptive systems for resolving inflammation, ultimately leads to hampering of behavioral parameters, quality of life as well as sleep and indices of metabolic as well as cardiovascular health. This may result in development of ‘systemic anti-inflammatory feedback’ and/or hyperactivity of the pro-inflammatory factors locally thereby contributing to pathogenesis of several diseases (Boulanger and Shatz, 2004; Jaremka et al., 2013).

Such kind of neuroimmunoinflammation as well as neuroimmune activation use to play role in the etiology of several neurodegenerative diseases viz., Parkinson’s as well as Alzheimer’s disease; along with dementia related to Acquired Immune Deficiency Syndrome (AIDS). If immunological or physiological and psychological challenges are absent, the CNS activities can also be modulated by cytokines as well as chemokines (Elenkov et al., 2005; Heneka and O’Banion, 2007).

With consistent observation of neurogenesis in the hypothalamus of adult mice, a key question has been raised namely whether there is relevance of neurogenesis in the hypothalamus to metabolic diseases. There is indeed a relation between reduction in arcuate neurogenesis and dietary obesity as well as obesity induced by leptin deficiency. It has been shown that the arcuate nucleus contains less new neurons than older neurons. Neuronal loss can give rise to hypothalamic neurodegeneration in case of obesity. In case of obesity therefore hypothalamic neurodegeneration can arise from loss of neurons and reduction of neural regeneration that arises from impairment of neural stem cells. It has also appeared that only certain kinds of neurons are having susceptibility to such kind of injury thereby giving rise to modest neuronal losses which may prove to be insufficient for affecting several neurological functions which are classical in nature. By nature, proopiomelanocortin (POMC) neurons have got less population but possess essential metabolic functions which are regulatory in nature leading to development of metabolic diseases (Cai, 2013).

NEUROIMMUNE CROSS TALK

Neuroimmune interaction is bidirectional. Immune systems talk-back to the nervous system and modulate the functions thereby on its own system. This is termed as neuroimmune cross talk (Silverman, 2005). Both systems share common mediators synthesized by the both systems, act on the common receptors. Physiological outcome depends on their action on either or both the system. A mediator secreted from one system can affect the other system. e.g., Substance-P secreted from the nerve cells can stimulate the lymphoid proliferation, mast cell degranulation and cytokine secretion and may block T-cell adhesion. C-fibres previously thought to have free nerve endings, now known to have association with dendritic cells, Langerhan cells and mast cells. The nervous system consistently associates with the immune system and controls its function through neuroendocrine or neurocrine mechanism. There must be a scheme in immune system that sends signals to nervous system to inform the current status of it. Various experiments showed that secreted products of immune cells such as cytokines and products of mast cells degranulation give sensory stimuli to the nerves. Sensory nerves also respond to external stimuli by antigen through an Antigen Presenting Cell (APC), chemo-sensor, a photoreceptor or hair cells and no specific mechanisms are needed for them to detect antigen as in case of specific immune cells (Shepherd et al., 2005). Vagus, a mixed nerve has important role in neuroimmuno crosstalk. It expresses receptors for interleukins to sense immune stimuli from periphery and communicates to the CNS. Thus sectioning of vagus nerve ablated the CNS induced sickness behaviour in lipopolysaccharide (LPS) injected mice which confirmed the vagal involvement in central transmission (Blithe et al., 1994).

Above all, the nervous system requires immune system for the normal development. The severe combined immunodeficiency (SCID) mice with impaired immune system showed defective neural development and impaired learning and memory. The similar findings were observed with the germ free mice and mice with depleted CD4+ T cells (Kipnis et al., 2004; McGowan et al., 2011; Wolf et al., 2009). Exercise to the muscles has influence on immunomodulation. Sensory stimulus to the soleus, an antigravity muscle of hind limb, increases the expression of CCL20 chemokine via adrenergic nerves. This chemokine changes the architecture of the vasculature at the fifth lumbar cord, so that immune cells can enter into the CNS. Sensory stimulation to different muscles activates different regions of the nervous system and helps in neural immunity. But in case of autoimmune disorders this
allows the entry of pathogenic immune cells and helps in disease development (Arima, 2012). Another circuit exercise pressor reflex is activated during exercise through the mechanoreceptors or chemoreceptors present in the muscles and the reflex will be descended through presynaptic cholinergic nerves conveyed to adrenergic nerves post synaptically. Adrenergic nerves innervate many smooth muscles and its activation does not always end in inflammation but there may be mechanisms to modulate it. For example exercise reduces the cardiovascular disease burden by increasing the vagal output and decreasing circulatory concentrations of TNFα, IL-6 and C-Reactive Protein (CRP) (Andersson and Tracey, 2012). Infiltration of immune cells into the Central Nervous System (CNS) is observed in case of several neurological diseases. Sharing of mediators employed by immune cells in the CNS are involved in promotion of crosstalk between neuronal and immune cells and on the context of the interaction, much of the net effect of this neuro-immune cross-talk depends. In several experimental paradigms, it has been proven that there may be augmentation of tissue injury in the CNS, mediated by inflammatory reactions. It has been however suggested through emerging evidences that there may be contribution to neuro-protection as well as repairs by the inflammatory cells. This is a dual function of the inflammation of CNS which has got reflection on the molecular level. It is due to the fact that it has become increasingly clear that both neuro-destructive as well as neuro-protective molecules can be released by immune cells into the lesions of the CNS. This maintains destructive and protective factors’ balance ultimately determining the net result of the interaction (neuro-immune) (Kerschensteiner et al., 2009, 2010).

Chiropractic medicine, an alternative medicine deals with curing musculoskeletal disorders by manual therapy. It started first with Spinal Manipulative Therapy (SMT) and now it has being used in various fields such as sports medicine and lifestyle modification therapy (Keating, 2008). Another alternative medicine called acupuncture deals with curing of diseases by stimulating various acu-points with needles (Cabyoglu et al., 2006). Both these modalities have the basis of nerve stimulation. Stimulation of sensory nerves with specified frequency stimulus induces immune responses with neural memory.

**STRESS AND NEUROIMMUNOMODULATION**

HPA axis forms the primary stress management system of the body thereby responding to physical as well as mental challenge for maintaining homoeostasis through control over the cortisol level of the body. In several diseases related to stress there is implication of the dysregulation of the HPA axis. It has been found that various types and duration of stressors along with unique personal psychological variables can dictate the HPA response. Inflammatory cytokines stimulate the adrenocorticotropic hormone (ACTH) along with secretion of cortisol, leading to inhibition of the synthesis of pro-inflammatory cytokines (Herbert and Cohen, 1993; Elenkov et al., 2005).

Not only stress due to pathogens but also stress from other causes including mental stress said to have influence on the neuro-modulation. Prolonged stress continuously activates CNS thereby causing priming of the microglia. Stress sensed by CNS not only affects the immune and endocrine system but also affects the cardiovascular system. There was a high correlation between patients diagnosed with cardiovascular disorders and mood affections. Cardiovascular diseases (CVD) produce depression in patients; similarly the patients with CVD had previous episodes of depression. In human beings, environmental stress (mental stress) like work overload, marital conflicts, health problems etc., greatly impact the alterations in the neurochemical functions. Chronic stressors cause degenerative nervous disorders, depression and result in the CVD and susceptibility to the infection (Grippo and Johnson, 2009). Studies on aged animal models revealed exacerbated inflammatory responses, cognitive impairment and defective learning behaviour. Ageing reduces the threshold for the activation of microglial cells and aged individuals are susceptible to the neurodegenerative disorders. Increased inflammatory responses by aged brain have been in part mediated by primed microglia and astrocytes. In aged brain there is dysfunction of neuroinflammatory control and resistance to the inflammation was reduced. As a consequence, a smaller stress can amplify the glial cells activation and progression in neurodegeneration. This is manifested as mental derangement, cognitive impairment, depression, sickness behaviour and impaired coordination between CNS and peripheral organs (Norden and Godbout, 2013).

Various studies have recommended Yoga for its multiple benefits to reduce stress and also to modulate the immune system. Yoga acts on both hypothalamus and also on the sympathetic nervous system. By acting on the sympathetic nervous system it can cause catecholamine increase leading to metabolic and central venous system effects. Similarly, by acting on hypothalamus Yoga induces release of various hormones which modulate immunity (Arora and Bhattacharjee, 2008). Physical activities have also been assessed for their neuro-immunomodulatory functions. The studies revealed that physical activities like aerobics, flexibility, resistance and motor activities can lead to neuro-immune modulation (Eyre and Baune, 2014).

**NEUROIMMUNOMODULATION AND AGING**

In the process of immune response, inflammation is considered as a protective phase. An intrinsic part of the brain’s physiological activity is the repair mechanism. The brain’s microenvironment is an important player in determination of the contribution (relative) of the two entirely different outcomes. The molecular as well as cellular mechanisms that sustain the brain repair programme if fails
may prove to be a cause of neurological disorders. At present, the neurotoxic as well as neuroprotective roles of the immune reactions (which are innate in nature) in the process of aging are highly debated research topics (Gemma, 2010). There is a correlation between neurogenesis in adult as well as learning as evidenced by several lines. The inflammation of the brain is involved in the reduction of neurogenesis in the hippocampus between microglia and neurons which are age related in nature. Neuronal or microglial signaling dysfunction leads to a state, priming inflammation and neurotoxicity mediated by microglia. Two important neuro-immunomodulator molecules viz., fractalkine and CD200 are responsible for such kind of communication. Any kind of hampering or interruption in the neuronal or microglial signaling results in impairment of neurogenesis in the hippocampus along with memory function (Gemma et al., 2010). During the process of aging, inflammation influences plasticity in the synapses. It has been shown by conducting experiment that when an aged animal is challenged with bacteria or virus or if surgery is performed in the brain, there is an aggravated inflammatory response. When aged animals are peripherally treated with lipopolysaccharide (LPS) on exposure to a spatial as well as contextual memory task, there is a more deficit in long term memory in comparison to the corresponding young animals. The inflammatory cascade in the aging process involves the active participation of IL-1β and subsequently activation of MAP kinases (p38) (Barrientos et al., 2010). Calcineurin is involved in several neuronal (or non-neuronal) and physiological functions and plays an important role in physiological aging. It acts as an enzyme which is bidirectional in nature; there is an importance of the balance of bidirectional effects in the process of aging. Hyperactivity of calcineurin causes cognitive function deficit along with neuroinflammation, enhancing the process of aging (Reese and Tagialatela, 2010).

The microglial cells are entirely beneficial and so also supportive for maintenance of homeostasis in the CNS. Over last few years there have been extensive researches which have led to the development of interesting theory of ‘microglial senescence’. This has helped in understanding that with age microglia becomes dysfunctional leading to higher susceptibility to infection of brain as well as enhancement of susceptibility to neurodegeneration. There may be mitotic ability losses after various replication rounds. There are evidences of presence of abnormal microglia (or otherwise known as dystrophic microglia) in the aged human brain, whose morphology is entirely different from that observed in aged rodent microglia (Streit and Xue, 2010).

**NEUROINFLAMMATION AND NEURODEGENERATION**

A two-way communication between the neuroendocrine and immune system is modulated by inflammation and inflammatory responses. Several researches have been conducted which established various routes through which there could be a communication between the immune system and central nervous system. The immune system is signaled by the CNS via hormonal pathways including the hypothalamic-pituitary-adrenal axis as well as hormones of the neuroendocrine stress response via neural pathways that include the autonomic nervous system. Immuno regulatory roles are also played by the sex hormones as well as by hypothalamic-pituitary-gonadal axis. The CNS is signaled by the immune system through mediators of immunity as well as cytokines crossing blood-brain barrier. They may signal indirectly via vagus nerve or also through second messengers. Immune function regulated by the neuroendocrine system, helps in stress survival or infection and for modulating immune responses in inflammatory diseases (Eskandari et al., 2003).

Neuroinflammation is a response of brain to an injury or infection or insult caused by any means. In general, inflammation is a process to repair or heal the injury and remove damaged tissues and pathogens but in central nervous system, inflammation is degenerative. The reasons are, brain is located in a closed cage made of skull bones and inflammation allows free flow of fluids and leucocytes. This results in increased skull volume which would exert pressure on neurons (Campbell et al., 2012; Ballestero-Zebadua et al., 2012). Secondly, inflammatory cytokines from any source can activate microglial cells and astrocytes. A variety of causes are responsible for initiation of neuro-inflammation that include infection, brain injury (traumatic), metabolites (toxic) or autoimmunity. Microglia are the resident innate cells of the immune system in the CNS including brain and spinal cord. CNS is a typical immunologically privileged site as there is blocking of the immune cells at the periphery by the blood brain barrier (astrocytes as well as endothelial cells constitute this specialized structure). A compromised blood brain barrier may be surpassed by the circulating peripheral immune cells which perpetuates the immune responses. The effect may be toxic in nature even though there is initiation of the response for protecting the central nervous system. It ultimately may result in wide spread inflammation resulting in leukocytes’ migration further through the blood brain barrier (Gendelman, 2002; Hart and den Dunnen, 2013; Sarma, 2014). Microglia is the first cell to respond to the insult. It constantly surveys the neural environment and it secretes a large amount of inflammatory and anti-inflammatory cytokines upon sensing an insult. There is a tipping balance between neuro-protection and degeneration. Initially activated microglia acts as neuro-protectant but in prolonged/subsequent stimulation (priming), the effects are more devastating to neural cells than protection (Harley and Tizabi, 2013). Several mechanisms have been described about stress mediated neuro-inflammation. Stress releases large amount of excitatory neurotransmitters such as glutamate and aspartate. Released glutamate bind to N-Methyl D-Aspartate (NMDA) receptor subtype expressed in CNS, this raises the intracellular calcium...
Increased intracellular calcium in turn activates many calcium dependent enzymes and finally ends in protein misfolding, cytoskeletal damage and free radical generation, called as excitotoxicity. The neurons and astroglia express high affinity transporters for the glutamate transport and hence susceptible to excitotoxicity. Activation of NMDA subtype of glutamate receptor enhances the release of TNFα, a major cytokine that activates NFκB, a nuclear transcription factor; activation of this causes transcription of several proinflammatory cytokines and genes responsible for oxidative and nitrosative products. Among them nitric oxide synthases and cyclooxygenases are responsible for production of NO, a free radical gas and eicosanoids, modulators of inflammation, respectively (Munhoz et al., 2008). There are also concerns about overnutrition induced neural inflammation. Over nutrition activates the proinflammatory gene, kappa B nuclear factor (NFκB) expression in hypothalamus, this activates the neuro-inflammation through cytokine signaling and initiating oxidative stress, leading to impaired neuro-humoral transmission, autophagy, loss of regulatory neurons and impaired neural regeneration. Neural impairment causes changes in regulation of autonomic energy balance, leading to the development of obesity, diabetes and cardiovascular disorders (Cai, 2013). It is important to note that following injury there is release of inflammatory factors like chemokines (sustained release) leading to compromised blood brain barrier. This increases the permeability of the blood components and immune cells at the periphery. Then there may be entry of macrophages as well as T and B cells which are involved in the innate as well as adaptive immune responses. Ultimately there is exacerbation of the brain’s inflammatory environment thereby contributing to neuroinflammation as well as neurodegeneration at chronic stage.

Over the past few years, research has been conducted on neuroendocrinology as well as immunology revealing that neuroinflammation induced by over nutrition is as essential pathological component that leads to a variety of dysfunctions. It happens in the CNS in case of obesity as well as metabolic diseases found in relation to it. It has got negative impact on neuro-hormonal signaling of neurons of the hypothalamus along with neurodegeneration is influenced by inflammation induced by over nutrition. For such neurodegenerative disorder, disruption of hypothalamic neural stem cell as well as pro-inflammation molecules such as kappa B nuclear factor is responsible mechanistically. The scenario of obesity and related diseases is affected by the link between obesity related inflammation and neurodegeneration. Additionally, a mechanistic hint has been found to be emerging that underlies the relation between metabolic diseases induced by over nutrition and Alzheimer’s or Parkinson’s like neurodegenerative diseases (Thaler and Schwartz, 2010; Cai and Liu, 2011).

Over the past few decades, research has focused on peripheral tissue examination that is relevant to the obesity and related diseases’ pathogenesis. They include skeletal muscle, liver as well as fat as the metabolic sites are represented by them which are responsible predominantly for utilization of nutrients and storage. Several metabolic dysfunctions in the peripheral tissues are related locally to inflammation. From the epidemiology, clinical medicine as well as experimental research, it is evident that obesity (along with other related diseases) is indeed found in association with low-grade inflammation (which are chronic in nature) in tissues of the periphery as well as in the circulation. In the CNS there is induction of I kappa B kinase due to chronic over nutrition. Especially in the hypothalamus, a change may contribute to several over-nutrition related disease developments (Cai, 2012).

Neurodegeneration is the end result of the inflammatory process. It starts with death of nerve cells and their clearance from the system. It may be considered as healing process but this may not be the case always, because pathogenesis of many of the neurodegenerative diseases starts with the autoimmune induction. Microglia, the resident immune cells of the CNS, mediates the neurodegeneration but its action is tightly controlled by the microenvironment of the CNS. However, prolonged stress or repeated stimuli from antigens, xenobiotics, trauma and incomplete clearance of misfolded proteins activate (priming) the microglia. Primed microglia are susceptible to secondary inflammatory stimuli (e.g., senility) arising from the CNS (Perry and Holmes, 2014). Persistent inflammation or impaired control mechanism keeps the microglia in active state for prolonged period. Excessive activation of microglia secretes lot of neurotoxic factors, among them, NOX2 is considered to be a common and essential factor for the microglial directed neurotoxicity. NOX2 subfamily of NADPH oxidase enzymes are highly expressed in phagocytic cells like neutrophils, microglia and also expressed in other cell populations. Microglial NOX2 is a chronic source of free radical super oxide anion, either itself or after dismutation to hydroxyl radical causes the degeneration of surrounding neurons. Normally, neurons can modulate amount of ROS in CNS but some areas of brain are vulnerable to this raise. NOX2 also enhances the microglial responses to the diversified stimuli which contribute to the chronic magnified neurotoxic response of microglia (Surace and Block, 2012). Exosomes are filled in the endosomes formed by the invagination of endosomal limiting membrane. Although, definitive evidences are lacking, their significance in transmission of neurodegenerative diseases are discussed. Exosomes are recognized in carrying misfolded proteins of several neurodegenerative disorders including tau and amyloid-β peptide in Alzheimer’s disease, superoxide dismutase 1 (SOD1) in Amyotrophic Lateral Sclerosis (ALS), huntingtin in Huntington’s Disease (HD) and α-synuclein in Parkinson’s Disease (PD) (Schneider and Simons, 2013; Allen et al., 2014). Amyotrophic lateral sclerosis is a condition where there is problem in the voluntary motor neurons which paves path to atrophy of muscles, loss of weight and finally there is respiratory failure and death (Zhu et al., 2014). ALS
is familial with mutation seen in the copper zinc Super Oxide Dismutase 1 (SOD1) (Smith et al., 2012; Tortelli et al., 2013; Ajroud-Driss and Siddique, 2014).

Genetic mutations are responsible for several neurodegenerative diseases and most of them are found in location in genes which are completely unrelated. In several different diseases, a common feature has been found in the mutated gene: When the CAG trinucleotide sequence is repeated it gives rise to polyglutamine (polyQ) tract. The amino acid glutamine is encoded by CAG and the diseases originating from this are termed as polyglutamine diseases. By expanding the CAG trinucleotide as well as polyQ tract nine inherited neurodegenerative diseases may occur. Two best examples in this regard are Huntington’s disease and spinal cerebellar ataxias. In various neurodegenerative diseases, swelling of the axon as well as spheroids has been observed. This is suggestive of the fact that not only in diseased neurons, the defective axons are present but they may also cause certain pathological insults due to organelle accumulation. A variety of mechanisms can disrupt axonal transport thereby triggering Wallerian-like degeneration (De Vos et al., 2008; Coleman and Freeman, 2010).

The neurodegeneration process is not well-understood for some of the diseases which have no cure. Employment of animal disease models has been done for testing potential therapeutic agents in search of effective treatment. Dimebon (Medivation) is an example of the drug which in phase III clinical trials for Alzheimer’s disease and recently in phase II trials for Huntington’s disease. In a study a rat model of Alzheimer’s disease has been used to demonstrate administration of hypothalamic Proline-Rich Peptide (PRP)-1. Degradation of proteins has offered therapeutic options both in prevention of the synthesis as well as irregular protein degradation. Upregulation of autophagy may also be of interest for helping clearing aggregates of proteins that has implication in neuro-degeneration. Very complex pathways are involved in both these options that are understood well at present. The various aspects of the immune system are enhanced by immunotherapy which as the main goal. For Alzheimer’s disease and certain other conditions there have been proposals of both active as well as passive vaccinations. For proving the safety as well as efficacy in humans, more and more research studies must be carried out (Rubinsztein, 2006; Brody and Holtzman, 2008; Galcoyan et al., 2008).

It has been seen that there are numerous associations between neuroinflammation and neurodegenerative diseases. It has led to increased interest for determining whether reduction of inflammation will lead to reversal of neurodegeneration. There are evidences that decrease in inflammatory cytokines (viz., IL-1β) would decrease neuronal loss. Interferon-β, glatirameracet as well as mitoxantrone are included for treating multiple sclerosis currently. They function by reduction or inhibition of activation of T cells but have got immunosuppressive side effects. Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) as well as glucocorticoids function by the blockade of converting prostaglandin H2 into other prostaglandins and thromboxanes. There is an increase in microvascular permeability as prostaglandins as well as thromboxanes act as mediators of inflammation (McPherson and Anderton, 2013). Furthermore, histone deacetylase inhibitors like valproic acid (HDACs) and L-thyroxine are able to reduce multiple sclerosis by regulating immune responses in rodent models (Castelo-Branco et al., 2014).

NEUROIMMUNOMODULATORY DRUGS AND HERBS

Treatment of neurodegenerative and neuroinflammatory conditions is not so easily achieved because the damage caused by these degenerations cannot be reversed easily (Pope et al., 2014). Various studies reported that it could be possible to stop the disease process when the genes involved or the genes which have mutated are stopped from their expression (Zu et al., 2004; Furrr, et al., 2013). Trials with rat on amyotrophic lateral sclerosis revealed that preventing the expression of mutant gene lead to partial recovery of motor activities (Huang et al., 2012). Halting the mutant genes from expression can be done either by delivering antibodies which are synthesized (Gros-Louis et al., 2010; Liu, et al., 2012) or by gene silencing methodology using small interfering RNAs (siRNAs) (Rizvanov et al., 2009; Miller, et al., 2013).

There are drugs which have neuroimmunomodulatory activity. Opiate drugs are the major group that can modulate neuronal immunity. Various studies with several opiates have been conducted on this aspect of neuroimmunomodulation. Morphine is one such a drug which acts through opioid receptors that are sensitive to naloxone. Studies on hamster indicate that morphine can regulate the course of Leishmania donovani infection (Singal et al., 2002). Melatonin synthesized from pineal gland of all mammals has neuro-immunomodulatory effect as well as Natural Killer (NK) cell stimulant. Experiments with melatonin and Echinacea with leukemic mice showed elevation in the NK cell count (Miller, 2005).

Serotonin, an amine autacoids and neurotransmitter in CNS, has other functions to act as immuno-modulatory agent. Exogenous administration of serotonin or its metabolic blockade showed suppression of non-specific immune response and the inhibition of their receptors produced increased immune response. Thus, serotonin mediated activation of the nonspecific immune suppression gives complete control over the immune homeostasis. Dopamine, another neuroimmunomediator acts through D1 and D2 receptors to produce immune stimulation and blockade of the receptors produced opposite effect. Their concentrations vary with variable psycho-emotional status of the animal. Thus the effect of immuno-moduatory therapy with these drugs depends on concentration of the receptors in CNS (Idova et al., 2012). Pioglitazone is an anti inflammatory agent having neuroprotective properties that was used in studies against ALS in mice model and it yielded good results in extending the onset of disease process (Kiaei et al., 2005a; Schutz et al.,

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Antioxidants have an important role to play in preventing the neuro-degenerative diseases like stroke, Parkinson’s disease and Alzheimer’s disease (Rahal et al., 2014b). Various antioxidants have been studied for their effects in laboratory animal models against ALS. DP-109, a metal chelator and MB0, an iron chelator, were found to increase the survival of the animals with ALS (Petri et al., 2007; Kupershmidt et al., 2011). Caffeine present in coffee and theophylline present in tea has neuro-modulating properties (Ross and Petrovitch, 2001). Studies conducted with animals showed that caffeine which is an antagonist of adenosine A (2A) receptor, improves movements in animals with Parkinson’s diseases (Chen et al., 2001). Similarly, theophylline acting as an antagonist of the same receptor like caffeine also improves locomotor activity.

Several herbs are used worldwide as neuroimmunomodulatory agents. Echinacea is one such herb of the family Asteraceae. Echinacea has various chemical components which have been proved to have stimulatory activity on immune system (Miller, 2005). Various active ingredients present in grapes and Chinese herbs like Polygonum cuspidatum have antioxidant properties and hence have good neuro-protective properties. Though nicotine present in cigarette prevents Parkinson’s disease but cigarette smoking is not advisable (Tan et al., 2003). Curcumin, the active component of turmeric has various useful properties like anti-inflammatory, anti-tumour and antimicrobial properties. Curcumin also has neuro-protective functions. Curcumin having anti amyloid property is useful in Alzheimer’s disease condition (Ringman et al., 2005). Amyloid-beta peptides (Abeta) are targeted by curcumin; it also prevents activation of microglial cells and cytokine production (Wang et al., 2005). These properties help to prevent amyloid deposition in brain, leading to reduced incidence of Alzheimer’s disease. Scutellaria baicalensis flowering plant of family Lamiaceae has various health beneficial components as its active principles. Baicalein, baicalin and wogonin are few examples of active principles having neuro-protective properties (Lee et al., 2003). Wogonin reduced lipopolysaccharide (LPS) induced release of TNFα, thereby reducing the level of inflammation in the brain cells hence acting as anti-inflammatory and neuro-protectant (Cho and Lee, 2004). A Chinese herb Ginseng belonging to family Araliaceae has also been evaluated for the

VITAMINS AND MINERALS AS NERVOUS SYSTEM MODULATORS

Vitamin D is biologically inert and its bioactivation involves hydroxylation on carbon number 25 in the liver. The 25-hydroxyvitamin D-1-alpha-hydroxylase activity gets down regulated by 1, 25 D thereby leading to tight controlling of the blood 1, 25-D. Oxidation of the side chain catalyzes both 1, 25-D as well as 25-D in kidneys by oxidizing the side chain by vitamin D-24-hydroxylase. Numerous target genes’ expression is regulated by 1, 25D via vitamin D receptor at nucleus. The mechanism of action of vitamin D is similar to that of steroid hormones. Vitamin D performs the role of autocrine as well as paracrine neuro active steroid. Drugs in relation to vitamin D may be used as a preventive therapy thereby causing minimization of the risk of developmental as well as various other related disorders of brain viz., schizophrenia. Vitamin D has immense immune-modulating characteristics thereby implying its potential role in the neuro-immune interaction. There has been indeed implication of low vitamin D status in the autoimmune disease etiology viz., multiple sclerosis; rheumatoid arthritis; diabetes mellitus which is dependent on insulin as well as inflammatory bowel disease. If there is very low environmental supply of vitamin D, there is very high prevalence of multiple sclerosis that strengthens the role of this hormone potentially as a natural inhibitor of multiple sclerosis. Metabolism of 25-D in an autocrine or paracrine fashion; alteration in macrophage as well as dendritic and T cell functions; in apoptotic signals their
sensitization along with certain action on the CNS component of pathogenesis of multiple sclerosis are the main factors contributing to the anti-multiple sclerotic role of vitamin D (Kaluff et al., 2006). Use of vitamin D3 (cholecalciferol) has been found to be essential for protection of the myelin sheath and preventing multiple sclerosis in case of mice. Vitamin D in its neural form is otherwise known as vitamin D3. A 5000 International Unit (IU) of vitamin D3 is found to be best according to several researchers. In forming myelin sheath, vitamin B-12 also plays a crucial role. The myelin sheath may be strengthened by lecithin which has been found to be one of the crucial building blocks of the membranes of the neurons wherein there is a cell to cell communication. Low level of vitamin B3 (niacin) and vitamin B6 can lead to severe headaches as well as stress. This problem can be counteracted by vitamin B complex. Both vitamins B3 as well as B6 can be supplemented by protein rich foods viz., beans, nuts, chicken and fish. Plasma atomic emission spectroscopy and atomic absorption spectrophotometry have been used to compare the trace mineral concentrations between healthy horses and horses with Equine Motor Neuron Disease (EMND) in the spinal cord. It has been found that the concentration of copper is significantly higher in the horse’s spinal cord with EMND in comparison to control horses. For all other trace minerals, the spinal cord concentration has been found to be similar between the groups. It has been hypothesized that in this disease, oxidative injury is supported by the finding of copper concentration at increased level in the spinal cord and by low concentration of vitamin E as reported by other researchers (Polack et al., 2000). Vitamins like vitamin A and vitamin C; vitamin E as well as vitamin B12 along with minerals viz., zinc and calcium; selenium as well as magnesium are crucial elements to stimulate immune responses. Nerve tonics as well as digestive tonics are helpful for strengthening and for feeding nervous tissues (Yanagihara, 1982).

VOLATILE OILS AS NERVE TONICS

One of the rich sources of volatile oil is peppermint which must be selected by a professional for helping choosing the correct concentration and herb types for using as stimulants and they must not be taken without recommendation (Erdegrul, 2002).

CONCLUSION

Nerves connect almost all the body systems and control every function of the cell. They also communicate with the...
immune system through the chemical mediators and control the immune function. The communication between nervous and immune systems is bidirectional, since the immune system sends back signals to nervous system through various cytokines and sensory nerves. Usually, nervous system signals for the inflammation and neuroprotection in a controlled fashion. There is a tipping balance between neuroprotection and degeneration. Exaggerated immune stimuli activate the microglial priming and primed microglia secrete a variety of inflammatory factors and oxidants which can damage the neurons. Etiology of several neurodegenerative disorders are related to the impaired neuroimmunomodulation due to the dysfunction of microglial cells. Till date, no effective drug is developed to cure these disorders, hence, targeting these neuromodulatory pathways may provide the way for new drug discovery and effective cure. There are several associations between neuroinflammation as well as neurodegenerative diseases that have led to increased interest for determination of inflammation reduction that ultimately may lead to reversal of neurodegeneration. Recently interferon-β, glatiramer acetate as well as mitoxantrone are included for treatment of multiple sclerosis which function by reducing or inhibiting T cell activation but also exhibit side effects like immunosuppression. In addition, L-thyroxine and HDACi have been tested in rats experimentally to control multiple sclerosis and should be tested for their effects in humans. Further research need to be conducted in the field of neuroimmunotherapy for precision of treatment. Vitamins like vitamin D3 as well as B complex; several heavy as well as trace minerals (that include copper, zinc, calcium as well as selenium); volatile oils etc., play crucial role in providing immunity to the central nervous system. Explorative research is required further to know their exact mechanisms of action in modulating the neural immunity. In the same fashion, a good knowledge of genetics is essential to understand the mechanism of occurrence of various neurodegenerative diseases and for formulating the therapeutic approaches to combat them.

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