Neuroimmunology

- Innervation of lymphoid organs
- Neurotransmitters
- Neuroendocrine hormones
- Cytokines
- Autoimmunity
Table 1.2 *Major anatomical divisions and subdivisions of the brain*

<table>
<thead>
<tr>
<th>Forebrain</th>
<th>Brainstem</th>
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<td>Telencephalon</td>
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<td>Cerebral hemispheres</td>
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<td>Amygdala</td>
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<td>Hippocampus</td>
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<td>Basal ganglia</td>
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<td>Septum</td>
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<td>Diencephalon</td>
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<td>Thalamus</td>
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<td>Hypothalamus</td>
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<td>Midbrain</td>
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<tr>
<td>Hindbrain</td>
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<td>Medulla</td>
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<td>Cerebellum</td>
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<td>Pons</td>
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</table>
CNS has two ways of contacting and regulating structures in the periphery

- Autonomic outflow
- Neuroendocrine outflow
Brain and the immune system are involved in functionally relevant cross-talk; main function is to maintain homeostasis.

Autonomic Nervous System:
· Regulates the function of all inervated tissues and organs in the body except the skeletal muscle fibers
· Autonomous or independent – its activities are not under direct conscious control
· Three components: sympathetic (noradrenergic) system
  parasympathetic (cholinergic) system
  enteric system
· Sympathetic – originates in nuclei within the brain stem and gives rise to nerve fibers (preganglionic fibers) that leave the CNS and terminate in ganglia in the spinal cord. From ganglia the postganglionic fibers innervate the tissues
Criteria for Neurotransmission by Noradrenergic Nerves

- Presence and localization of nerve fibers
- Release of neurotransmitter
- Presence of receptors for neurotransmitter
- Functional role for neurotransmitter
Growth Hormone

- Augments in vitro proliferation of lymphocytes
- Thymocytes, resting lymphocytes and monocytes express high affinity receptors
- IL-1 augments systemic release
- Deficiencies associated with abnormal cellularity of thymus and bone marrow, depressed T cell function, NK activity and antibody responses
Neuroendocrine Effects of Cytokines

**IFN-α/β**
- Adrenal-steroidogenesis
- Induction of melanin synthesis
- Excitation of neurons
- Catalepsy and analgesia

**IL-1**
- Fever
- Promotion of slow-wave sleep
- Hypothalamic release of CRF
- Pituitary release of ACTH
- Elevation of glucocorticoid levels

**IL-2**
- Pituitary release of ACTH
- Elevation of glucocorticoid levels
Brain – An Immunologically Privileged Site?

Absence of a conventional lymphatic system
  -Interfere with afferent arm of immune response to CNS antigen

Presence of blood-brain barrier
  -Block efferent arm by preventing entrance of effector cells and molecules of the immune system into the brain

Absence of antigen-presenting cells
Brain – An Immunologically Privileged Site?

- Injection of Ag into CNS – Ag-specific serum Ab response and Ab-secreting cells have been found in cervical nodes and spleen
- Activated T cells have capacity to enter the CNS
- Intrathecal Ab synthesis occurs
- Class II MHC expression can be induced on astrocytes and microglia cells

Immune Privilege – an active not passive state associated with antigen-specific suppression of cell mediated and humoral immunity

TGF-β a potent immunosuppressive cytokine is present in extracellular fluid

Expression of Fas ligand equips site to delete by apoptosis Fas+ T cells that enter the CNS. Lack of Fas ligand expression may interfere with immune privilege
Neurologic Diseases with an Immune Component

CNS
Multiple sclerosis, Sjogren’s, acute disseminated encephalomyelitis, SLE, paraneoplastic syndromes, stiff-man, AIDS

PNS
Guillain Barre, paraneoplastic syndromes, leprosy, polyneuropathy

Neuromuscular Junction
Myastenia gravis, Lambert-Eaton syndrome

Muscle
Polymyositis, dermatomyositis
Myastenia Gravis

- Prototype of all autoimmune diseases
- Characterized by weakness of voluntary muscles – eye closure, face, chewing, swallowing
- Etiology – unknown
- Affects younger women (20s) and older men
- Autoantigen is the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction
- 90% of patients have anti-AChR antibodies
- IgG binds to the endplate causing a reduction of AChR and simplification of the postsynaptic region of the endplate. Postsynaptic area is flattened – synaptic clefts are shallow – reduced neuromuscular transmission
- Therapy – corticosteroids, thymectomy, plasmapharesis
Guillain-Barre Syndrome

- Acute, demyelinating disease of the peripheral nervous system

- Incidence 1-2/100,000

- Multiple triggering events – cytomegalovirus, Epstein-Barr virus, mycoplasma

- Believed to be primarily antibody mediated, although cell mediated abnormalities have also been observed

- IL-2, IL-6 and TNF-α levels are elevated

- Gangliosides are strong candidate target autoantigens

- Therapy – plasma exchange, intravenous immunoglobulin
Etiology of Multiple Sclerosis

- Environmental factor
- Familial tendency
- Susceptibility gene
- Suspect virus
- Autoimmune reaction
Evaluation of Morphological Progression in MS
Serial MRIs: Same Lesion Enlarging

Courtesy of Donald W. Paty, MD.
Evaluation of Morphological Progression in MS
Serial MRIs: Same Lesion Fading

Courtesy of Donald W. Paty, MD.
MULTIPLE SCLEROSIS

- Inflammatory disease of the central nervous system
- Afflicts approximately 250,000 young adults in the USA
- Affects the myelin sheaths surrounding the nerve fibers resulting in demyelinating plaques
- Etiology and pathogenesis are unknown

ENVIRONMENTAL
- Virus or microbial agent triggers disease onset
- Latitude effect - north - south gradient
- Migration studies - exposure in early adolescence

GENETIC
- Major predisposing genes - HLA DR15 and DQw6
- Ten fold higher concordance rate for MS in monozygotic twins
- Increased incidence in females compared to males 2:1
- Familial and racial occurrence
AUTOIMMUNE FEATURES OF MS

- Lymphocytes and macrophages are present in areas of demyelination
- Decrease in number and function of CD8+ T cells
- Decrease in NK cell activity
- Increase in CD4/CD8 T cell ratio
- Oligoclonal immunoglobulin bands in cerebrospinal fluid
- T cells specific for certain myelin antigens have been found with increased frequency
- Immunosuppressive therapies have beneficial effect
Interferon beta-1b
Rationale for Use in MS

- Mechanism for beneficial effect in MS not established
- Viral infections provoke MS attacks; Interferon beta-1b is an antiviral agent
- Inhibits synthesis of IFN-γ, TNF, and LT in vitro and possibly in vivo
- Increases suppressor T-cell function in MS patients
- Directly counteracts peripheral effects of IFN-γ on target cells (i.e., adhesion molecule induction and class II MHC induction by IFN-γ)
- Inhibits lymphocyte proliferation
- Induces immunosuppressive cytokines, i.e., TGF-β1
Interferon beta-1b: Clinical Efficacy in MS
Disease Activity in 52 Patients (Based on MRI Scans)

Active Scans (%)

30
20
10
0

Placebo (n=17)

0.25 mg (8 million IU) Interferon beta-1b (n=17)

p=0.006

Official Prescribing Information for Betaseron® (Interferon beta-1b) for SC Injection.
Interferon beta-1b
Clinical Efficacy: Primary Efficacy Endpoints

Reduction in Exacerbation Rates\textsuperscript{36}

<table>
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<th>Exacerbation Rates</th>
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<td>Annual Exacerbation Rate</td>
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- Fewer exacerbations in patients treated with Interferon beta-1b
- Greatest reduction in exacerbations with 0.25 mg (8 million IU) Interferon beta-1b (vs placebo; p = .0001)
Interferon beta-1b
Mechanism of Action

- Overall mechanisms of action are not fully elucidated

- Binds to a specific cell surface receptor²⁶
  - Interferon beta-1b is highly species specific, binding only to receptors in humans and monkeys

- Internalizes into cell via receptor-mediated endocytosis²⁷

- Induces the expression of specific proteins via a number of transcription factors²⁶

- Proteins code for specific cell surface antigens and intracellular enzymes that mediate immunologic, antiproliferative, and antiviral effects²⁶