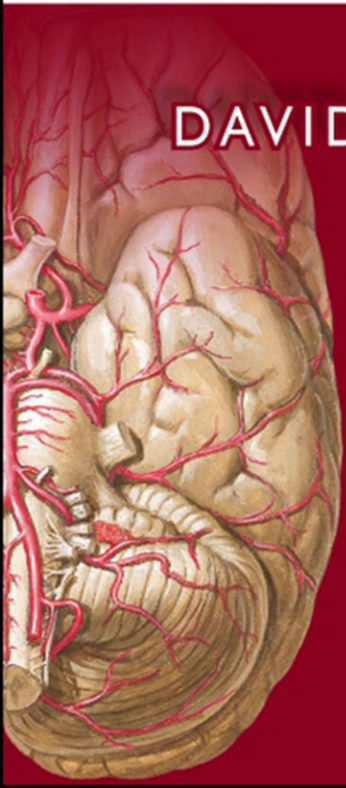
NETTER'S
NEUROSCIENCE FLASH CARDS

3rd Edition

DAVID L. FELTEN



F. Netter M.D.

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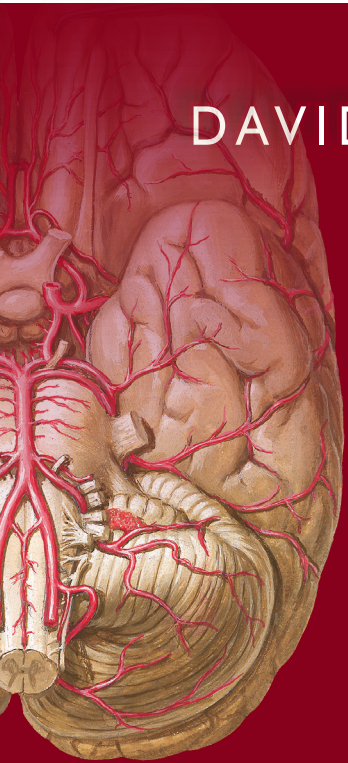

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THIRD EDITION

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Acknowledgments

Netter's Neuroscience Flash Cards, third edition, is a logical follow-up to *Netter's Atlas of Neuroscience*, third edition. Both publications are intended to provide a visually oriented, succinct roadmap to the basic neurosciences and their application to human disease and its treatment. I have thoroughly enjoyed working with Marybeth Thiel (Senior Content Development Specialist), Elyse O'Grady (Senior Content Strategist), and John Casey (Senior Project Manager) from Elsevier in the long and challenging process of producing the *Flash Cards* and *Atlas*. Their helpfulness, diligence, professionalism, and commitment to bringing the Netter illustrations to yet more generations of physicians and health care professionals are inspirational. I thank Jim Perkins, the outstanding medical illustrator who worked closely with the authors of the third edition of *Netter's Atlas of Neuroscience*; his skillful and accurate work have helped us to include extensive new information on molecular and cellular neurosciences. I also gratefully acknowledge the mentorship and wonderful teaching of former Professor Walle J.H. Nauta, MD, PhD, from the Massachusetts Institute of Technology; his superb organization of the nervous system, brilliant insights, and use of overviews inspired generations of neurosciences researchers, educators, and practitioners. I gratefully acknowledge the love, support, and encouragement of my wife, Dr. Mary Maida, who continues to tolerate mountains of books and papers piled all over the house and office while we worked on the Netter projects.

And finally, I acknowledge the inspiration that my mother, Jane E. Felten, provided through her long challenge with the aftermath of polio. Although she was badly crippled by the disease at the age of 8, she never let this neurological disease interfere with living a full and happy life. Her example demonstrates that human determination, will power, and faith can be powerful motivators for successful living, and that the indomitable human spirit can overcome even the most daunting challenges. Jane Felten demonstrated one of the fundamental principles of medicine—that one can be truly healed even in the face of severe pathology and disease and in the absence of a "cure." She fought the good fight and lived a rich and rewarding life for more than 70 years. This project is dedicated to her memory.

Preface

Netter's Neuroscience Flash Cards, third edition, consists of selected illustrations from *Netter's Atlas of Neuroscience*, second edition, published in 2009. In this third edition I have deleted some of the previous flash cards and added many new ones from illustrations in the third edition of *Netter's Atlas of Neuroscience,* published in 2016. Reference to the corresponding figure number in the *Atlas* can be found on the front of each card. Relevant structures are labeled on the front of each flash card illustration with 1, 2, 3 and so forth. On the back of the flash card is a list of all labeled structures. In some instances, such as the illustration of the cranial nerves, the schematic of hypothalamic nuclei, or the limbic forebrain structures, the labels are comprehensive enough to include all of the major components, providing students an opportunity to test their knowledge in a more thorough fashion than with just a few labels.

In addition to the list of labeled structures, the back of the flash card also includes a comment. The comments consist of two types of information: (1) organizational information about the illustration that provides a summary of the structure or system whose components are labeled on the front (e.g., a brief summary of visual system projections and their functional role on the flash card demonstrating the extent of retinal projections); (2) brief discussion of points of clinical relevance to the illustration on the front of the flash card. Approximately half of the flash cards have comments that address the former, and half have clinical comments. The choice of comments on the back was determined by the author's consideration of what type of information would be most useful to a student trying to master the challenging field of neuroscience. *Netter's Atlas of Neuroscience,* third edition, contains extensive clinical comments, in contrast to the first edition. For the more detailed clinical points, the *Atlas* itself is the appropriate source.

Students have the delightful habit of asking challenging questions related to illustrations—such as those used in *Netter's Atlas of Neuroscience*, third edition—and include, "So how does this fit in with big picture of how the brain works?" or "So why do I need to know this information?" As information resources continue to expand, the ability of students to become more selective in their time allocation, to review helpful summaries of information that are still thorough and accurate, and to succinctly learn about the clinical relevance of information to patient care, becomes more and more valuable. These flash cards provide assistance toward that end. However, I also remind my students that they need to know the underlying basic science principles and mechanisms so that the clinical relevance is a logical follow-up, not just a bunch more facts to memorize.

In preparing the flash cards for the third edition, I also took into account the wonderful new technology that enables the student to obtain iPod or iPhone downloads, useful both for studying or exam preparation, and for reviewing information of relevance to a specific patient with a neurological problem or symptom. I tried to provide sufficiently comprehensive information in the labeling, as well as a useful succinct summary, to allow the student to review or refresh information that can be useful in the consideration of a patient's diagnosis or evaluation.

The study of neuroscience ultimately requires the student to develop an understanding of the application of scientific knowledge to human illness and pathology. In medical school courses, clinical correlations and clinical examples are used to help students find the bridge between basic sciences and clinical application. *Netter's Atlas of Neuroscience*, third edition, and *Netter's Neuroscience Flash Card*s, third edition, have been written to optimize this process. Most students do not want to wallow through a 1,500 page textbook looking for relevant material buried in a seemingly endless discourse on esoterica. Until the student develops a solid overview of the field and is able to place structures, pathways, systems, symptoms, and neurological phenomena into proper context, the large reference works will be confusing and more trouble than they are worth. Most students want to cut to the chase and only later will they seek more detailed information when it becomes important in the care of a patient. These flash cards are designed to cut to the chase.

During my childhood, the use of flash cards was an enjoyable way to learn essential information and approaches. It is in this spirit that *Netter's Neuroscience Flash Cards* were developed. Students who have the persistence and drive to use these cards to review fundamental neuroscience with a strong slant toward succinct organization and clinical relevance will emerge with a surprisingly broad array of knowledge about major neurological applications of the basic sciences. They also will find themselves unusually well prepared for licensure and board certification examinations that require such knowledge. I wish the users of these *Flash Cards* and *Netter's Atlas of Neuroscience*, third edition, both success and enjoyment as they follow this visually-oriented learning format, and have the opportunity to benefit from the wonderful illustrations and medical knowledge of Dr. Frank Netter. It is the success of my students that makes the endeavor of teaching truly worthwhile.

David L. Felten, MD, PhD

Contents

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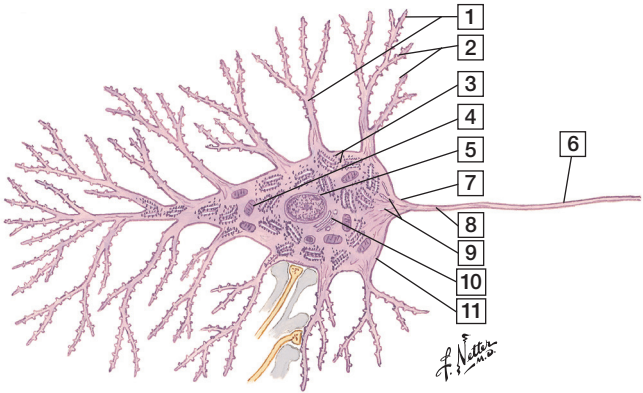
1 Overview of the Nervous System
Plates 1-1 to 1-64


1
2
3
4
5
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7
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9
10
11
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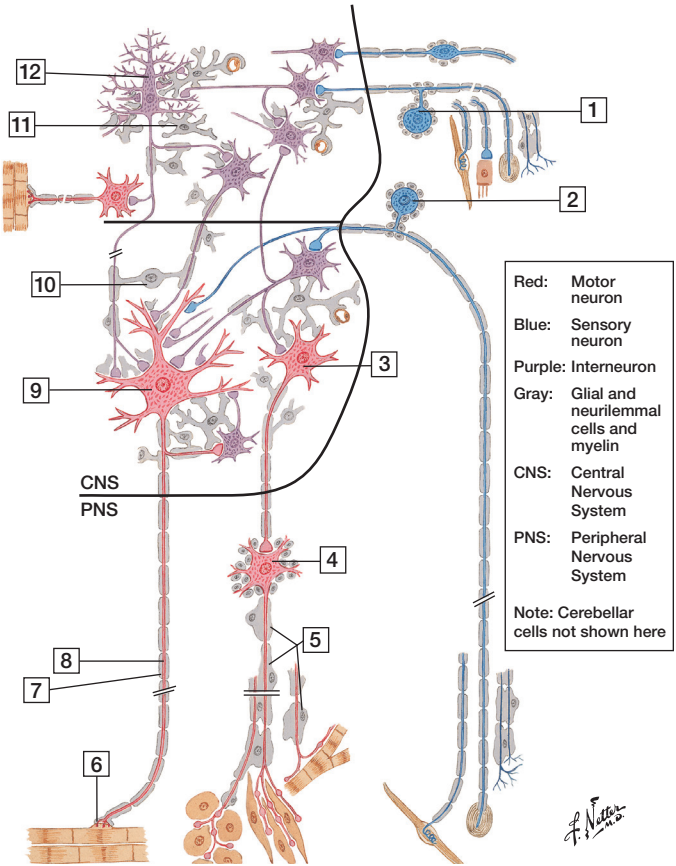
1. Dendrites
2. Dendritic spines
3. Rough endoplasmic reticulum
4. Mitochondria
5. Nucleus
6. Axon
7. Axon hillock
8. Initial segment of axon
9. Neurotubules
10. Golgi apparatus
11. Cell body (soma)

Comment: The neuron is a highly active cell metabolically, with great demands for oxygen and glucose related to aerobic metabolism, especially important for maintaining ion gradients across the neuronal cell membrane. Neurons have very little metabolic reserve and depend on moment-to-moment delivery of oxygen and glucose. Neuronal form is related to the function of each individual neuron. Dendritic arborizations reflect the expanse of the neuron related to gathering synaptic input from other neurons; these arborizations show some plasticity and can expand or regress, depending on the local neuronal microenvironment and the extent of input. The axon generally distributes to a relatively fixed set of specific target structures (neurons, muscle, and effector tissue) but also may expand or regress as dictated by demand. The internal state of gene expression is a snapshot of the specific demands to which the neuron is responding and may change according to hormonal or neurotransmitter signaling, or according to other molecular influences on transcription factors.


12
11
1
2
10
3
9
CNS
PNS
4
5
8
7
6
Red: Motor neuron
Blue: Sensory neuron
Purple: Interneuron
Gray: Glial and neurilemmal cells and myelin
CNS: Central Nervous System
PNS: Peripheral Nervous System
Note: Cerebellar cells not shown here
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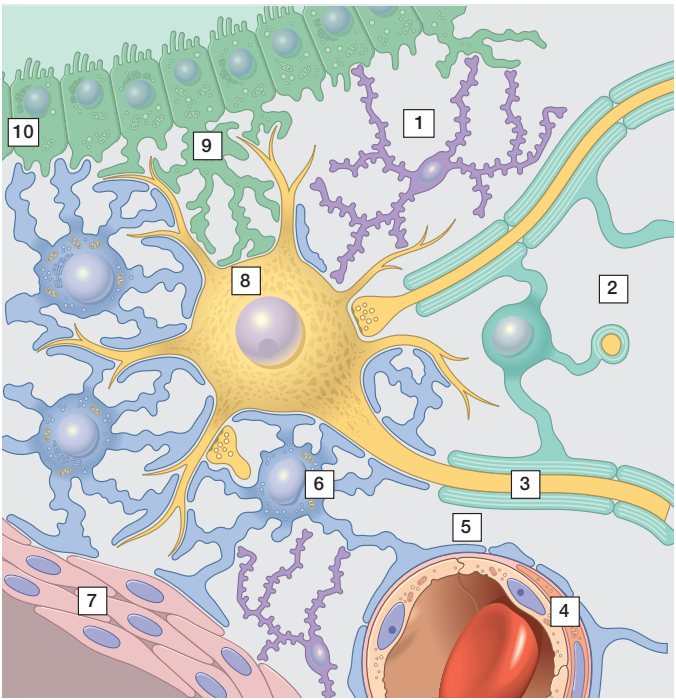
Neuronal Cell Types

1. Primary sensory unipolar ganglion cell of sensory cranial nerves
2. Primary sensory unipolar ganglion cell of dorsal root ganglion
3. Multipolar neuron (autonomic preganglionic neuron)
4. Autonomic ganglion cell
5. Schwann cell
6. Motor end plate (neuromuscular junction)
7. Myelin sheath
8. Myelinated motor axon
9. Multipolar neuron (spinal cord motor neuron)
10. Oligodendrocyte
11. Astrocyte
12. Multipolar neuron (pyramidal cell)

Comment: Neurons are organized into hierarchies. Incoming (afferent) information is transduced by sensory receptors associated with the distal portion of primary sensory neurons. These neurons convey the information into the central nervous system and synapse on secondary sensory neurons associated with reflex channels, cerebellar channels, and lemniscal channels, the latter of which is associated with conscious interpretation. Outputs from the central nervous system consist of (1) lower motor neurons, whose axons terminate on skeletal muscle fibers, forming neuromuscular junctions; and (2) preganglionic autonomic neurons of the sympathetic and parasympathetic nervous systems, whose axons synapse on ganglion cells that, in turn, regulate smooth muscle, cardiac muscle, secretory glands, metabolic cells, and cells of the immune system.

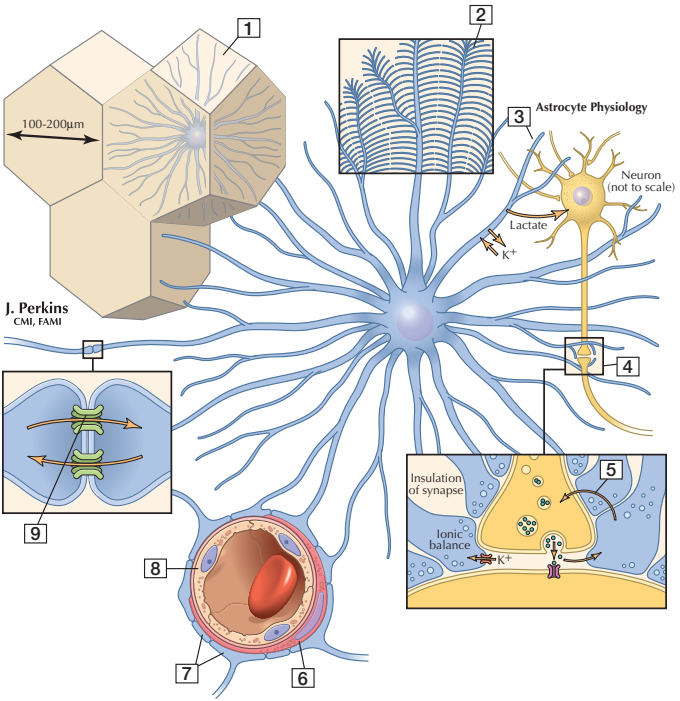


J. Perkins
MS, MFA

Glial Cell Types

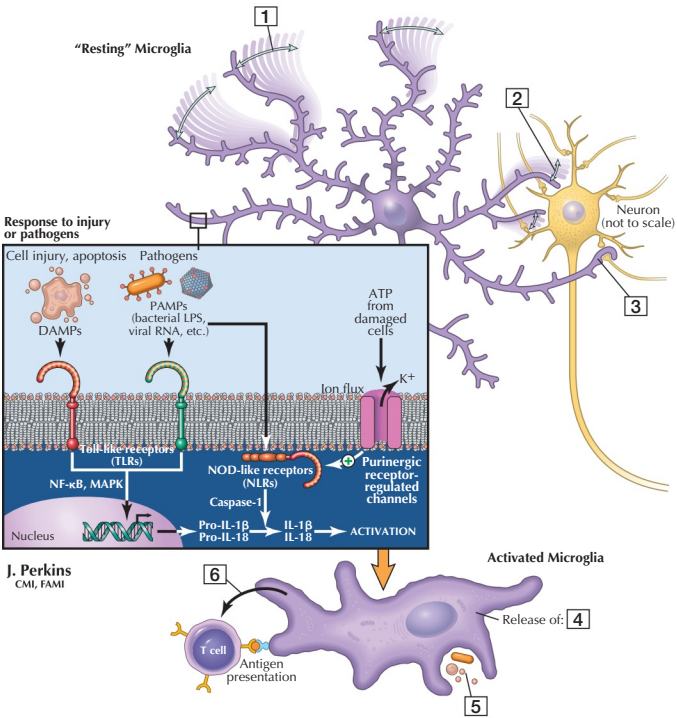
1. Microglial cell
2. Oligodendrocyte
3. Axon
4. Perivascular pericyte
5. Astrocytic foot process
6. Astrocyte
7. Pia mater cells
8. Neuron
9. Tanycyte
10. Ependymal cell

Comment: Glial cells provide the supportive cellular structure and function for neurons. They act as scaffolding between neurons, sequester ions (potassium), insulate synaptic sites, provide trophic and molecular support for neurons (astrocytic functions), provide myelination of axons (oligodendrocyte function), phagocytize debris, participate in inflammatory responses, present antigens, and provide other immunologic and cytokine reactivity (microglial functions). Approximately 10 times more glial cells exist than neurons. Glial cells are the principal cell types that proliferate to form CNS tumors; neurons rarely form tumors.


1
2
3
100-200µm
Astrocyte Physiology
Neuron
(not to scale)
Lactate
K+
J. Perkins
CMI, FAMI
4
5
9
Insulation
of synapse
Ionic
balance
K+
8
7
6

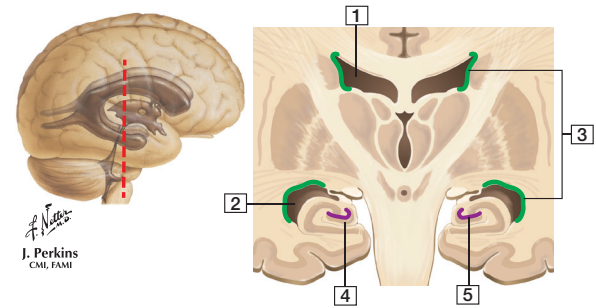
1. Astrocyte 3D domains
2. Bushy astrocyte processes
3. Metabolic support, ionic balance (K^+ sequestration), growth factor production, CNS gear formation
4. Synaptic myelination and isolation
5. Glutamate and GABA reuptake from a synapse
6. Vascular smooth muscle cell
7. Astrocytic end-foot process
8. Vascular endothelial cell
9. Gap junction between astrocyte processes

Comment: Astrocytes provide support and protection for neurons and their processes, synapses, CNS vasculature, and the inner meningeal pial-glial membrane. Astrocyte processes form an interdigitating syncytium to protect synapses and expand as end-foot processes to protect the blood-brain barrier. Astrocytes provide metabolic support for neurons, protect the ionic milieu, uptake and recycle glutamate and GABA, and release growth factors and bioactive molecules (gliotransmitters). After a CNS injury, astrocytes can lay down glial scar tissue; these scars may act as an irritating focus for provoking seizures. Astrocytes can also undergo transformation and proliferation to form invasive tumors, astrocytomas.


1
"Resting" Microglia
2
Neuron
(not to scale)
3
Response to injury
or pathogens
Cell injury, apoptosis
Pathogens
DAMPs
PAMPs
(bacterial LPS,
viral RNA, etc.)
ATP
from
damaged
cells
Ion flux
K+
Toll-like receptors
(TLRs)
NOD-like receptors
(NLRs)
Purinergic
receptor-
regulated
channels
NF-κB, MAPK
Caspase-1
Nucleus
Pro-IL-1β
Pro-IL-18
IL-1β
IL-18
ACTIVATION
J. Perkins
CMI, FAMI
Activated Microglia
6
Release of: 4
T cell
Antigen
presentation
5

1. Moving microglial processes
2. Microglial process sampling synapse
3. Synaptic remodeling
4. Reactive oxygen species ($\bullet O2^-$), reactive nitrogen species (NO), proinflammatory cytokines (IL-1, IL-6, TNF-α), matrix metalloproteinases, neurotrophic factors (NGF, TGF-β, neurotrophin 4/5, GDNF, FGF)
5. Phagocytosis of pathogens and cellular debris
6. T cell activation (cytokines)

Comment: Microglia are mesenchymally derived cells that act as scavenger cells in the CNS and participate in immune reactivity and inflammation in the CNS. Microglia can phagocytose cellular debris and pathogens and can remodel and remove synapses in developing and adult CNS. When activated by proinflammatory cytokines or other stimuli, microglia become ameboid in shape and secrete a host of reactive molecules (oxygen species, NO, proinflammatory cytokines, matrix metalloproteinases, and neurotrophic factors). Activated microglia can participate in and provoke T-cell related immune responses, particularly as T cells traverse the CNS.


1
2
3
4
5
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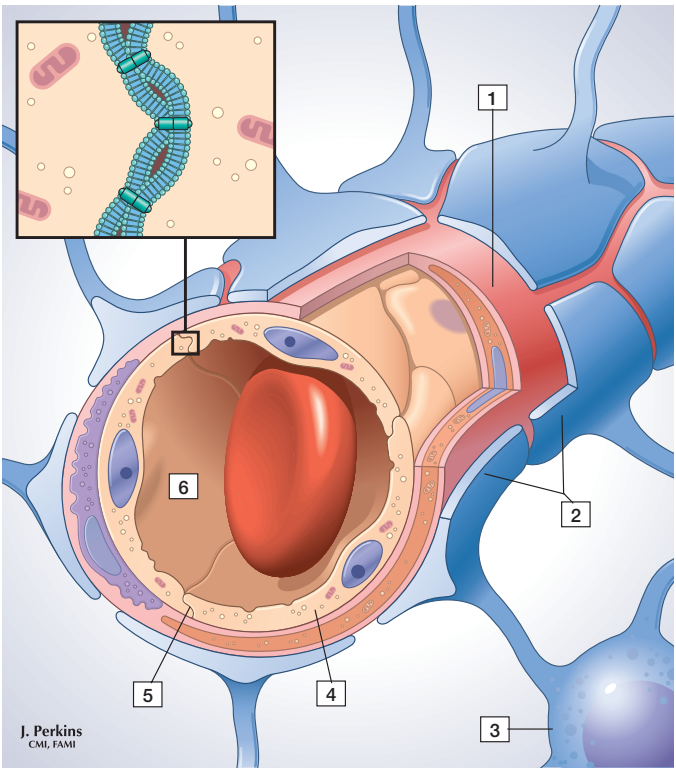
CMI, FAMI
I. Subventricular zone (SVZ) of lateral ventricle
6
Transient amplifying cells (C cells)
7
Asymmetric division
SVZ
Ependyma
Ventricle
Olfactory bulb
II. Subgranular zone (SGZ) of dentate gyrus
8
Type II progenitor cells
9
Asymmetric division
10
11
12
Spatial and episodic memory
Object recognition memory
Emotional regulation
III. Oligodendrocyte progenitor cells (OPCs)
OPCs widely distributed throughout adult brain and spinal cord (~5% of all cells in CNS)
NG2+ OPC
Myelin turnover
Myelin repair

1. Superior horn of lateral ventricle
2. Inferior horn of lateral ventricle
3. Subventricular zone (SVZ) of lateral ventricle
4. Dentate gyrus of hippocampus
5. Subgranular zone (SGZ) of dentate gyrus
6. Radial glia-like cells
7. Neuroblasts and migration route
8. Type I radial glia-like cells
9. Mature granule cell neuron
10. Subgranular zone (SGZ) of dentate gyrus
11. Granule cell layer
12. Molecular layer

Comment: In development, neuronal stem cells give rise to waves of proliferating and migrating neurons. In adulthood, stem cells are present in the subventricular zone of the lateral ventricles and can form neuroblasts, which can migrate to sites such as the olfactory bulb or zones of granular neurons, providing additional neurons. Stem cells in the subgranular zone can give rise to new granule cells. Oligodendroglial progenitor cells can give rise to new oligodendrocytes in response to demyelinating processes such as multiple sclerosis.

Externally derived stem cells have been used experimentally to treat spinal cord injury. These stem cells are used to attempt to replace damaged neurons or other cells or to produce trophic factors and growth factors that stimulate intrinsic repair and recovery.


1
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3
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5
6
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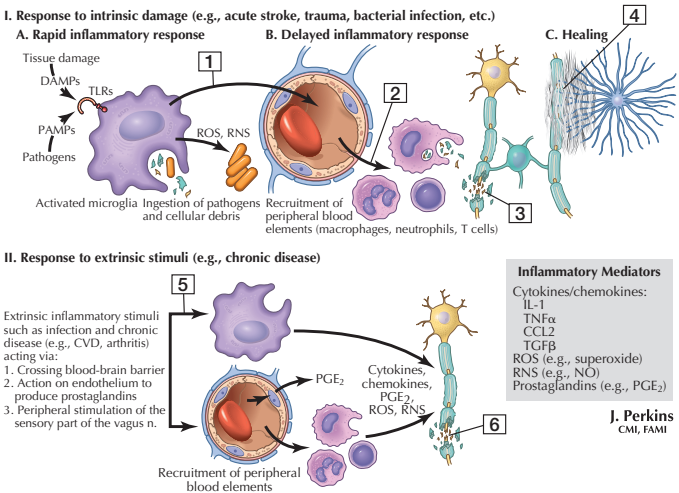
1. Basement membrane
2. Astrocytic foot process
3. Astrocyte
4. Capillary endothelial cell
5. Tight junction of endothelial cells
6. Capillary lumen

Comment: The major anatomical substrate for the blood-brain barrier (BBB) is the tight junctions of the capillary endothelial cells. They effectively keep large molecules out of the CNS and protect the brain from adverse effects of circulating toxins and potentially damaging molecules. Some substances can directly cross into the brain, others have a competitive facilitated transport (some amino acids), and others have an active transport system for ingress into the CNS. At sites of inflammation, tumors, trauma, and other insults to the brain, the BBB may be disrupted and allow damaging molecules into the brain. The effectiveness of the BBB prevents many therapeutic agents from having direct access to the brain and requires intraventricular or intrathecal delivery or coupling to a transport carrier.


I. Response to intrinsic damage (e.g., acute stroke, trauma, bacterial infection, etc.)
A. Rapid inflammatory response
B. Delayed inflammatory response
C. Healing
Tissue damage
DAMPs
TLRs
PAMPs
Pathogens
ROS, RNS
Activated microglia
Ingestion of pathogens and cellular debris
Recruitment of peripheral blood elements (macrophages, neutrophils, T cells)
1
2
3
4
II. Response to extrinsic stimuli (e.g., chronic disease)
Extrinsic inflammatory stimuli such as infection and chronic disease (e.g., CVD, arthritis) acting via:
1. Crossing blood-brain barrier
2. Action on endothelium to produce prostaglandins
3. Peripheral stimulation of the sensory part of the vagus n.
PGE2
Cytokines, chemokines, PGE2, ROS, RNS
Recruitment of peripheral blood elements
5
6
Inflammatory Mediators
Cytokines/chemokines:
IL-1
TNFα
CCL2
TGFβ
ROS (e.g., superoxide)
RNS (e.g., NO)
Prostaglandins (e.g., PGE2)
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III. Response to intrinsic proteinopathy or neurodegenerative process (e.g., Alzheimer disease)
Age-related "priming" of microglia
Activated microglia; Little or no recruitment of peripheral blood elements
Cytokines, chemokines
Slow, chronic inflammation with progressive synaptic dysfunction and loss of neurons
7
8
9
10

1. Cytokine and chemokine production
2. Breakdown of blood-brain barrier
3. Neuronal dysfunction and loss
4. Astrocytic scar formation
5. Activation of local microglia
6. Neuronal dysfunction and loss
7. Microglial ingestion of amyloid-β (Aβ) and tau protein
8. Aβ plaque
9. Tau neurofibrillary tangles
10. Astrocyte reactivity and loss

Comment: In response to intrinsic damage (e.g., acute stroke, trauma, bacterial infection), activated microglia and recruited peripheral blood immunocytes can precipitate neuronal dysfunction and loss and can provoke astrocytes to lay down scar tissue.

In response to extrinsic stimuli (e.g., infection, cardiovascular disease, arthritis), activated microglia and recruited peripheral blood elements can produce a host of inflammatory mediators that provoke neuronal injury and loss.

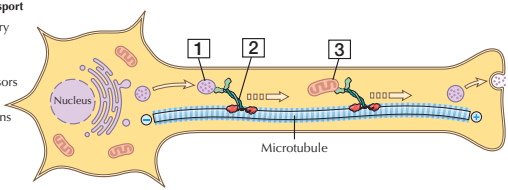
During an intrinsic proteinopathy or neurodegenerative process (e.g., Alzheimer disease), chronically activated microglia can ingest and degrade amyloid β (from Aβ plaques) and tau protein from neurofibrillary tangles, provoking astrocyte reactivity and loss, and chronic inflammation with synaptic dysfunction and neuronal loss.

Retrospective studies in patients with chronic arthritis have shown that prolonged ingestion of antiinflammatory drugs reduces the likelihood of Alzheimer-related dysfunction. Prospective studies have not been successful at reducing the likelihood of Alzheimer disease and its cognitive dysfunction, probably due to the long-standing duration of pathology and chronic inflammation by the time symptoms become evident and prospective therapy is initiated.

I. Fast Anterograde Axonal Transport

100–400mm/day in a saltatory fashion (start-stop-start)

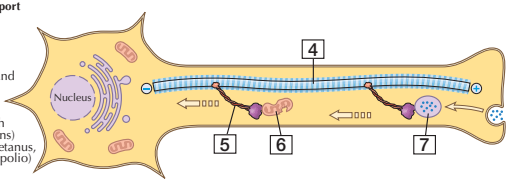
Cargo includes:
- Synaptic vesicles and synaptic vesicle precursors
- Mitochondria and other membrane organelles
- Integral membrane proteins
- Secretory polypeptides
- Neurotransmitters
- Elements of smooth endoplasmic reticulum



II. Fast Retrograde Axonal Transport

200–270mm/day

Cargo includes:
- Endosomes
- Damaged mitochondria and other organelles
- Elements of smooth endoplasmic reticulum
- Regulatory signals (growth factors and neurotrophins)
- Viruses and toxins (e.g., tetanus, herpes simplex, rabies, polio)

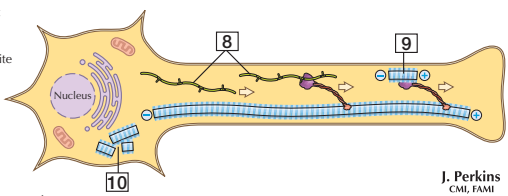


III. Slow Axonal Transport (Anterograde Only)

Different substances move at two different speeds:

Slow Component a (SCa)
0.2–2.5mm/day (rate of neurite elongation)
- Microtubules
- Neurofilaments
- Cytoskeletal proteins (e.g., α and β tubulin)

Slow Component b (SCb)
5.0–6.0mm/day
- Cytosolic proteins
- Clathrin
- Calmodulin
- Soluble enzymes and other proteins



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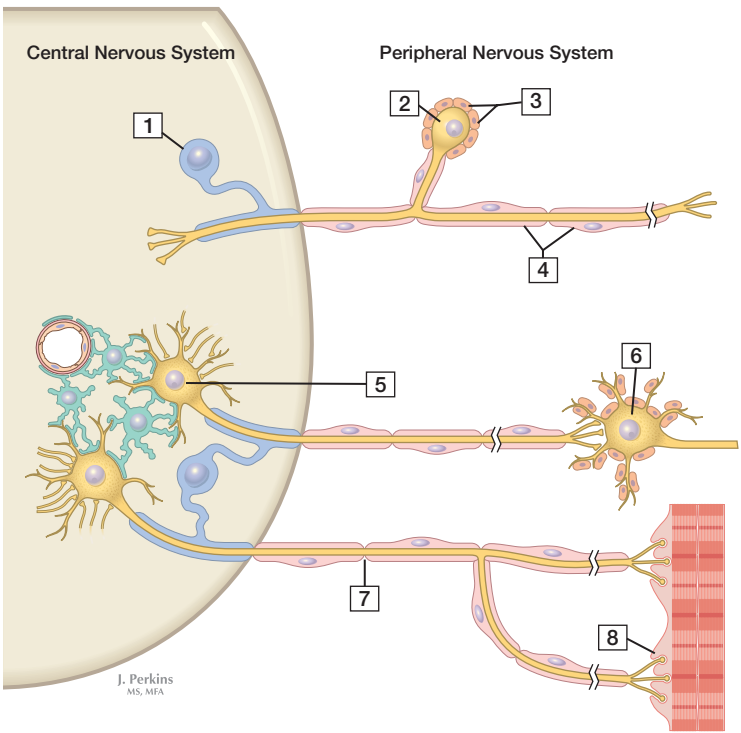
1. Vesicle
2. Kinesin
3. Membrane organelles
4. Microtubule
5. Dynein
6. Damaged organelles
7. Endosome
8. Neurofilaments move on own or carried along microtubules
9. Short segments of microtubules carried by dynein
10. Pre-assembly of microtubule segments

Comment: Neurons transport proteins, organelles, and other materials in both directions between the cell body and nerve terminals. Fast anterograde axonal transport, from cell body to nerve terminals, proceeds in a start-stop (saltatory) fashion, transporting synaptic vesicles, mitochondria, and organelles, smooth ER, integral membrane proteins, secretory polypeptides, and some neurotransmitters. Fast retrograde axonal transport, from nerve terminals to the cell body, transports endosomes, damaged organelles, growth factors and other proteins, viruses, and toxins. Polio virus takes advantage of this process to invade, damage, and sometimes kill lower motor neurons. Slow anterograde axoplasmic transport, with two separate components, transports microtubules and neurofilaments, cytosolic and cytoskeletal proteins, calmodulin, and other large molecules. This slow process is essential for damaged axons to regrow and reestablish their connections after insult or injury; as a consequence, such axonal recovery proceeds at a rate of approximately 1 mm/day.


Central Nervous System
Peripheral Nervous System
1
2
3
4
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6
7
8
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