1. Neurocellular Anatomy (provisional outline from BN6)

Cedric S. Raine

Understanding Neuroanatomy is Necessary to Study Neurochemistry (Figs 1-3)

Diverse cell types are organized into assemblies and patterns such that specialized components are integrated into a physiology of the whole organ

Characteristics of the Neuron (Figs 4-11)

General structural features of neurons are the perikarya, dendrites and axons

Neurons contain the same intracellular components as do other cell

Molecular markers can be used to identify neurons

Characteristics of Neuroglia (Figs 12-21)

Virtually nothing can enter or leave the central nervous system parenchyma without passing through an astrocytic interphase

Molecular markers of astrocytes.

Astrocyte functions

Oligodendrocytes are myelin-producing cells in the central nervous system

Molecular markers of oligodendrocytes.

The microglial cell plays a role in phagocytosis and inflammatory responses

Molecular markers of microglial cells.

Ependymal cells line the brain ventricles and the spinal cord central canal

The Schwann cell is the myelin-producing cell of the peripheral nervous system

References

2. Cell Membrane Structures and Functions

Wayne Albers

(Figures are numbered according to BN6)

Overview

Figure 2-1. Overview of plasma membrane structure.

Phospholipid Bilayers

Figure 2-2. Complex lipids interact with water and with each other to form different states of aggregation, or "phases".....

Functional importance of bilayer asymmetry.

Structure and functions of bilayer microdomains.

Lipid homeostasis (Figures)

.

Membrane Proteins

Figure 2-3. The transmembrane domains of integral membrane proteins ....

Figure 2-4. Left: Integral membrane proteins can be classified with respect to the orientation and complexity of their transmembrane segments. Right: Proteins may associate with membranes.....

Figure 2-5. The ankyrin-spectrin lattice.

Covalently attached lipids often participate in binding proteins to membranes.

Membrane Dynamics

Nascent membrane proteins must be inserted through the bilayer and transported to their destinations.

Figure 2-6. Initiation of membrane protein insertion into the endoplasmic reticulum (ER).

Figure 2-7. ..... the synthesis of polytopic membrane proteins

Figure 2-8. ... the transport of membrane components from one Golgi compartment to the next. This figure and some text is unnecessary if redundant with the trafficking chapter:

Figure 2-9. Endocytosis of membrane components...This figure and some text is unnecessary if redundant with the trafficking chapter...

BASIC NEUROCHEMISTRY, 7th EDITION

OUTLINE DRAFT 6/19/03

3. Lipids

Joyce A. Benjamins and Amiya K. Hajra

Introduction – ***add sentence about three major classes of lipids found in brain: phospholipids, sterols, and sphingolipids***

Properties of Brain Lipids

Lipids have multiple functions in the brain – ***add sentence on lipid rafts and role in signaling***

Membrane lipids are amphiphilic molecules

The hydrophobic components of many lipids consist of either isoprenoids or fatty acids and their derivatives

Isoprenoids have the unit structure of a five-carbon branched chain

Brain fatty acids are long-chain carboxylic acids which may contain one or more double bonds (FIGURE 3-1, STRUCTURES OF SOME FATTY ACIDS OF NEUROCHEMICAL INTEREST)

Complex Lipids

Glycerolipids are derivatives of glycerol and fatty acids (FIGURE 3-2, THE STRUCTURE OF PHOSPHOGLYCERIDES)

? consider omitting or using as supplementary material - TABLE 3-1, DISTRIBUTION PROFILE OF THE MAJOR MOLECULAR SPECIES IN THE DIACYLGLYCEROL MOIETIES OF RAT BRAIN PHOSPHOGLYCERIDES

In sphingolipids, the long chain aminodiol sphingosine serves as the lipid backbone (FIGURE 3-3, STRUCTURE OF SOME SIMPLE SPHINGOLIPIDS; FIGURE 3-4, A. STRUCTURE OF A GANGLIOSIDE, B. STRUCTURE OF SIALIC ACID), FIGURE 3-5, DIAGRAMMATIC REPRESENTATION OF TLC OF GANGLIOSIDES)

next page

Analysis of Brain Lipids

Shorten section on chromatographic separation, add paragraphs on mass spec analyis

Brain Lipid Biosynthesis

Acetyl coenzyme A is the precursor of both cholesterol and fatty acids

?consider omitting or using as supplementary material -FIGURE 3-7, PATHWAYS FOR INTERCONVERSION OF BRAIN FATTY ACIDS

Phosphatidic acid is the precursor of all glycerolipids (FIGURE 3-8, SCHEMATIC REPRESENTATION OF GLYCEROPHOSPHOLIPID BIOSYNTHESIS)

Sphingolipids are biosynthesized by adding head groups to the ceramide moiety (FIGURE 3-9, PATHWAYS FOR BIOSYNTHESIS OF SPHINGOLIPIDS)

"Lipidomics" – analysis of expression of genes and enzymes regulating lipid metabolism

Lipids in the Cellular Milieu

Lipids are transported between membranes

Membrane lipids may be asymmetrically oriented

Some proteins are bound to membranes by covalently linked lipids (BOX 3-1, GPI-ANCHORED PROTEINS - ***? any updates***

Lipids have multiple roles in cells – ***update roles in signaling, add paragraph on composition and formation of lipid rafts, refer to other chapters for discussion of roles of lipid rafts in protein trafficking and signaling; ?model of lipid raft or FRET image of raft on live cells may be in Chapter 2 (Albers)***

References

Possible web sites references (suitable? permission needed? frequency of updates?)

Crystal Structure of Glycerolipids - www.biochem.missouri.edu/-lesa/LIPIDS/lipid.html

Lipid Bank for the Web – lipid.bio.m.u-tokyo.ac.jp

The Lipid Data Bank (LDB) – www.ldb.chemistry.ohio-state.edu

4. MYELIN FORMATION, STRUCTURE AND BIOCHEMISTRY

Pierre Morell, Richard H. Quarles and Wendy Macklin

(This outline is based on the 6th Edition. Changes planned for the new edition are shown in ***blue***.)

THE MYELIN SHEATH

Myelin facilitates conduction

Myelin has a characteristic ultrastructure

Nodes of Ranvier

Schmidt-Lantermann Clefts

Myelin is an Extension of a Cell Membrane

Myelination in the PNS

Myelination in the CNS

Myelin affects axonal structure

Myelin can be isolated in high yield and purity by conventional methods of subcellular fractionation

CNS myelin isolation

PNS myelin isolation

CHARACTERISTIC COMPOSITION OF MYELIN

CNS myelin is enriched in certain lipids

PNS myelin lipids are similar to those of CNS myelin

CNS myelin contains unique proteins

Proteolipid protein

PLP gene family

Myelin basic proteins

Golli proteins

2'3'-Cyclic nucleotide-3'-phoshodiesterase (CNPase)

Myelin-associated glycoprotein (MAG) and other glycoproteins of CNS myelin

Other tetraspan proteins such as OSP/claudin, Mal, connexins

next page

Pathology associated with altered expression of PLP, MBP, CNP, MAG, connexins, and other tetraspan proteins.

PNS myelin contains some unique proteins and some shared with the CNS

P0 glycoprotein is the major PNS myelin protein

Myelin basic protein in the PNS

Peripheral myelin protein-22 (PMP-22) (describe in its own section rather than with other glyoproteins)

Other glycoproteins of PNS myelin (MAG, 170 kD glycoprotein, etc.)

Connexins

Pathology associated with altered expression of P0, PMP-22, MAG, and connexins

Proteins and structure of the nodal, paranodal and juxtaparanodal regions

Myelin contains enzymes and receptors that function in metabolism and ion transport.

DEVELOPMENTAL BIOLOGY OF MYELIN (shorten)

Myelination follows the order of phylogenetic development

The composition of myelin changes during development

Myelin subfractions may represent transitional forms of myelin

SYNTHESIS AND METABOLISM OF MYELIN (shorten extensively to one or two paragraphs)

Synthesis of myelin components is rapid during deposition of myelin

Some lipids and proteins must be transported to the site of myelin assembly

Myelin components exhibit great heterogeneity of metabolic turnover

MOLECULAR ARCHITECTURE OF MYELIN

REFERENCES

5. Membrane Transport

R. Wayne Albers and George J. Siegel

Neurophysiological aspects of transmembrane transport

A major fraction of cerebral energy production is required for extrusion of intracellular Na^+ that enters during excitation and secondary transport

Rapid clearance of K^+ from the extracellular space is critical because high extracellular K^+ depolarizes neurons

An outwardly directed Cl^- pump is necessary for the inhibitory, that is, hyperpolarizing, functions of GABA and glycine-gated ion channels

Intracellular pH in brain is regulated by Na^+,H^+ antiporters, anion antiporters and Na^+, HCO_3^- symporters

Cell-volume regulation involves control of the content of osmotically active impermeant molecules and ions

ATP-dependent transport

The P-type transporters.

The Na^+,K^+ Pump.

Coupled active transport of Na^+ and K^+ results from a cycle of conformational transitions of the transport protein

Differential localization of isoforms.

Post-translational regulation

The Ca^{2+} Pumps

ATP-dependent Ca^{2+} pumps and Na^+,Ca^{2+} antiporters act in concert to maintain low cytosolic free Ca^{2+}.

Other P-Type Cation Transporters

next page

V-type transporters ***Vacuolar ATP-dependent proton transporters occur in Golgi-derived membranes including presynaptic vesicles.***

ATP-Binding Cassette Proteins. ***The ATP-binding cassette proteins are members of the ABC superfamily with functions that encompass transport, ion conductance and post-translational regulation.***

ABCA1 and ABCA2 roles in CNS cholesterol and lipid transport.
ABCA4 (ABCR) role in retinaldehyde transport.

Secondary Transport Systems

Diverse transport functions are driven by energy obtained from the Na^+ and H^+ concentration gradients that are generated and maintained by the P- and V-type cation transporters.

Neurotransmitter uptake into presynaptic vesicles
Reuptake of released neurotransmitters.
Na^+, Ca^{2+} antiporters
Anion Antiporters.

"Uncoupled Transporters"

References

6. ELECTRICAL EXCITABILITY AND ION CHANNELS

Bertil Hille and William A. Catterall
hille@u.washington.edu wcatt@u.washington.edu *Running title: Excitability and Ion channels*

Plan: **Keep essential content of the former first three sections, but combine them into two Sections and condense wherever possible to make room for more modern material at the end. Also condense the beginning of the new Section 4 below, add Section 5, and expand Section 6 as outlined below.**

1. MEMBRANE POTENTIALS AND ELECTRICAL SIGNALS IN EXCITABLE CELLS

a. Excitable cells have a resting membrane potential (a condensed version of previous material from: How do membrane potentials arise? and Equilibrium potential is membrane potential at which there are no net ion movements)

b. Real cells are not at equilibrium

c. Electrical signals recorded from cells are basically of two types: stereotyped action potentials characteristic of each cell type and a variety of slow potentials

d. Transport systems also may produce membrane potentials

2. ACTION POTENTIALS IN ELECTRICALLY EXCITABLE CELLS

During excitation, ion channels open or close, ions move, and the membrane potential changes

Permeability changes of the action potential

Gating mechanisms for Na^+ and K^+ channels in the axolemma are voltage dependent

The action potential is propagated by local spread of depolarization

Membranes at nodes of Ranvier are characterized by high concentrations of Na^+ channels

A wide repertoire of voltage-sensitive channels is found among cell types

3. FUNCTIONAL PROPERTIES OF VOLTAGE-GATED ION CHANNELS

Shorten this section but keep the essential content

Ion channels are macromolecular complexes that form aqueous pores in the lipid membrane

Voltage-dependent gating requires voltage-dependent conformational changes in the protein component(s) of ion channels

Pharmacological agents acting on ion channels help define their functions

4. MOLECULAR COMPONENTS OF VOLTAGE-GATED ION CHANNELS

Shorten the early part of this section by combining and shortening the material under the first two headings

Neurotoxins were used as molecular probes to identify Na^+ channels

Primary structures of Na^+-channel subunits **were** determined using cDNA cloning

Ca^{2+} channels have a similar structure to Na^+ channels

K^+ channels were identified by genetic means

How do the primary structures of the ion channel subunits serve to carry out their functions?

5. STRUCTURAL BASIS FOR ION CHANNEL FUNCTION

X-ray crystallography of bacterial potassium channels reveals the structure of the pore

A possible gating mechanism for the pore

6. ION CHANNEL DIVERSITY

Na^+ and Ca^{2+} channel family members have different physiological roles

Nav1, Cav1, 2, 3, and trp channels here

K^+ channels are remarkably diverse

Kv channels here including eag, KCNQ, etc.

K^+ channels have many relatives

Kca, CNG, HCN, Kir, K2p here

There are many other kinds of ion channels

Ion channel diversity is increased by association with intracellular signaling proteins that modulate channel function