<<< Click on Bookmarks tab ^ Select "Full Width" display ^

BN7 outline & index to chapter outlines (*Last update = Wed, May 5, 2004*):

Black text = BN7 authors confirmed. Black chapter numbers = BN6 when different in BN7.
Red text = - as yet unresolved or not confirmed. Red chapter numbers = BN7 numbering.

Part One. Cellular Neurochemistry and Neural Membranes

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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

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...

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

8. CYTOSKELETON OF NEURONS AND GLIA

Scott T. Brady ***stbrady@uic.edu***

Molecular Components of the Neuronal Cytoskeleton

The cytoskeleton is one of several biological elements that define eukaryotic cells

Microtubules act as both dynamic structural elements and tracks for organelle traffic

Neuronal and glial intermediate filaments provide support for neuronal and glial morphology

Actin microfilaments and the membrane cytoskeleton play critical roles in neuronal growth and secretion

Ultrastructure and Molecular Organization of Neurons and Glia

A dynamic neuronal cytoskeleton provides specialized functions in different regions of the neuron

Both the composition and organization of cytoskeletal elements in axons and dendrites become specialized early in differentiation

go to next page

Cytoskeletal Structures in the Neuron Have Complementary Distributions and Functions

Microfilament and microtubule dynamics underlie growth cone motility and function

The axonal cytoskeleton may be influenced by glia

Levels of cytoskeletal protein expression change after injury and during regeneration

Alterations in the cytoskeleton are frequent hallmarks in neuropathology

Phosphorylation of cytoskeletal proteins is involved in both normal function and neuropathology

Conclusions

References

12. Catecholamines

Michael J. Kuhar, Kenneth P. Minneman, E. Christopher Muly

I. Biosynthesis of Catecholamines
- A. Tyrosine hydroxylase is the rate-limiting enzyme for the biosynthesis of catecholamines
- B. DOPA decarboxylase catalyzes the removal of the carboxyl group from DOPA to form dopamine
- C. For neurons that synthesize epinephrine or norepinephrine, dopamine β-hydroxylase is the next step in the biosynthetic pathway
- D. In cells that synthesize epinephrine, the final step in the pathway is catalyzed by the enzyme phenylethanolamine *N*-methyltransferase

II. Storage and Release of Catecholamines
- A. Catecholamines are concentrated in storage vesicles that are present at high density within nerve terminals
- B. The concentration of catecholamines within nerve terminals remains relatively constant
- C. Monoamine oxidase and catechol-*O*-methyltransferase are primarily responsible for the inactivation of catecholamines
- D. The action of catecholamines released at the synapse is terminated by diffusion and reuptake into presynaptic nerve terminals

III. Anatomy of Catecholaminergic Systems
- A. Cell bodies of noradrenergic neurons are clustered in the medulla oblongata, pons and midbrain and are considered to be anatomically part of the reticular formation
- B. Large numbers of cell bodies of dopamine-containing neurons are located in the midbrain

IV. Catecholamine Receptors, Pharmacology and Signal Transduction
- A. The brain contains multiple classes of receptors for catecholamines

V. Dopamine Receptors
- A. Multiple dopamine receptor subtypes exist
- B. The number of D1 and D2 receptors can be modulated by antagonists or neurotoxins
- C. Dopamine receptors are implicated in psychosis and its treatment

VI. _- and β-adrenergic Receptors
- A. The pharmacological responses to catecholamines were ascribed to effects of _- and β-adrenergic receptors in the late 1940s
- B. The amino acid sequences of β-adrenergic receptors in brain and various tissues have been determined
- C. Two families of _-adrenergic receptors exist

VII. Dynamics of Catecholamine Receptors
- A. Changes in the number of receptors appear to be associated with altered synaptic activity
- B. Changes in the number of dopamine receptors may also be involved in pharmacological actions of neuroleptic drugs
- C. Exposure of cells to agonists results in diminished responsiveness, referred to as desensitization

13. Serotonin for Basic Neurochemistry, Seventh Edition

J. G. Hensler

A. SEROTONIN

1. Historical Overview

"The indolealkylamine 5-hydroxytryptamine, serotonin, was identified initially because of interest in its cardiovascular effects".

Figure 1: Chemical structures of 5-hydroxytryptamine and related indolealkylamines..

2. Neuroanatomy of Central Serotonergic Systems

"Understanding the neuroanatomical organization of serotonergic cells in brain provides insight into the functions of the neurotransmitter".

Table 1: Classification of serotonergic cell body groups

Figure 2: Schematic drawing depicting serotonergic cell body groups and projections in sagittal section of rat brain.

Figure 3: Serotonergic cell bodies in midbrain raphe nuclei demonstrated by immunocytochemistry.

Figure 4: Diagram illustrating main features of dual serotonergic systems innervating forebrain.

3. Synthesis, Storage and Release of Serotonin

"The amino acid L-tryptophan serves as the precursor for the synthesis of 5-hydroxytryptamine".

Figure 5: The biosynthesis and catabolism of serotonin.

"The synthesis of 5-hydroxytryptamine can increase markedly under conditions requiring a continuous supply of the neurotransmitter".

"As with other biogenic amine transmitters, 5-hydroxytryptamine is stored primarily in vesicles and released by an exocytotic mechanism".

Figure 6:The substituted amphetamine fenfluramine inhibits both (a) the vesicular transporter and (b) the serotonin transporter (SERT).

4. The Serotonin Transporter

"The activity of 5-hydroxytryptamine in the synapse is terminated primarily by its re-uptake into serotonergic terminals".

will include "transporter promiscuity" e.g.5-HT taken up by the Norepinephrine transporter (NET) and the regulation of SERT function acutely by activation of terminal 5-HT_{1B} autoreceptor.

Figure 7: Putative structure of the rat serotonin transporter showing homologous amino acids with the rat dopamine transporter (DAT), human norepinephtrine trasporter (NET).

next page

5. Catobolism of Serotonin

"The primary catabolic pathway for 5-hydroxytryptamine is oxidative deamination by the enzyme monoamine oxidase".

6. Volume transmission and a neuromodulatory role for serotonin in the brain

"Consistent with a neuromodulatory role for serotonin, is evidence for volume transmission of this neurotransmitter".

will include extra-synaptic localization of the serotonin transporter, extra-synaptic localization of the terminal 5-HT_{1B} autoreceptor, the presence in serotonergic neurons of MAO-B, for which serotonin is not the preferred substrate, and localization of MAO-A to other neurons.

B. SEROTONIN RECEPTORS

1. Receptor Classification: Historical Perspective and Current Classification Criteria

"Pharmacological and physiological studies have contributed to the definition of the many receptor subtypes for serotonin."

Table 2: Serotonin receptors present in the CNS.

"Molecular biological techniques have led to the rapid discovery of additional serotonin-receptor subtypes and their properties."

a. 5-HT_1 receptor family

b. 5-HT_2 receptor family

c. 5-HT_3 receptors

d. 5-HT_4, 5-ht_6, and 5-HT_7 receptors

e. 5-ht_{5A}, and 5-HT_{5B} receptors

2. Receptor Distribution in Brain

"The many serotonin receptor subtypes are differentiated by their localization in the central nervous system."

3. Regulation of Receptor Function

"Many serotonin receptor subtypes do not appear to undergo compensatory regulatory changes."

next page

C. SEROTONIN INVOLVEMENT IN PHYSIOLGICAL FUNCTION AND BEHAVIOR

1. Behavioral arousal and activity

"Serotonin may set the tone of brain activity in relationship to the state of behavioral arousal/activity".

2. Circadian rhythmicity, neuroendocrine function and feeding

"Serotonin may set the tone of brain activity in relationship to the state of behavioral arousal/activity".

3. Serotonin is the precursor of the hormone melatonin

"Serotonin not only has important physiological effects of its own but also is the precursor of the hormone melatonin".

D. SEROTONIN NEURONS AND RECEPTORS AS DRUG TARGETS

Figure 8: The effects of psychoactive drugs on serotonergic neurotransmission.

14. HISTAMINE: THE MESSENGER AND THE MOLECULE

for Basic Neurochemistry, 7th edition
L. Hough and R. Leurs

Histamine is a mediator of several physiological and pathological processes within and outside of the nervous system.
The chemical structure of histamine has similarities to the structure of other biogenic amines, but important differences also exist.

HISTAMINERGIC CELLS OF THE CNS: ANATOMY AND MORPHOLOGY

The brain stores and releases histamine from more than one type of cell.
Histaminergic fibers originate from the tuberomammillary region of the posterior hypothalamus.
Histaminergic neurons have morphological and membrane properties that are similar to those of neurons storing other biogenic amines.
Histaminergic fibers project widely to most regions of the central nervous system.
Histaminergic neurons are present in many species.

DYNAMICS OF HISTAMINE IN THE BRAIN

Specific enzymes control histamine synthesis and breakdown.
Several forms of histidine decarboxylase may derive from a single gene.
Histamine synthesis in the brain is controlled by the availability of L-histidine and the activity of histidine decarboxylase.
Histamine is stored within and released from neurons, but no evidence for active neuronal re-uptake has been discovered.
In the vertebrate brain, histamine metabolism occurs predominately by methylation.
Neuronal histamine is probably methylated outside of histaminergic nerve terminals.
The activity of histaminergic neurons is regulated by H3 autoreceptors.

Next Page

MOLECULAR SITES OF HISTAMINE ACTION

Histamine acts on four G protein-coupled receptors, three of which are clearly important in the brain.

H1 receptors are intronless GPCRs linked to Gq and Ca mobilization.

(One or more Pars (RL): H1 molecular, signalling and regulation)

Par (LBH): H1 conductances and electrophysiology

H2 receptors are intronless GPCRs linked to Gs and cyclic AMP synthesis.

One or more Pars (RL): H2 molecular, signalling and regulation.

Par (LBH): H2 conductances and electrophysiology

Both positive and negative interactions may occur between H1 and H2 receptors.

H3 receptors are a family of GPCRs produced by gene splicing and linked to Gi/o.

One or more Pars (RL): H3 molecular – gene structure and splicing

One or more Pars (RL): H3 signalling, brief pharmacology of polymorphisms?

Par (LBH): Localization of H3: autoreceptors and heteroreceptors – LBH

Par (LBH): H3 conductances and electrophysiology

Par (?): H3 receptors are constitutively active in vivo

H4 receptors are very similar to H3 receptors in gene structure and signal transduction, but may not exist in the brain.

Short par by RL on everything you want to say immune/inflammatory cells?/ splice variants?

Histamine can modify ionotropic transmission at identified and unidentified sites

One Par (LBH) – modification of NMDA and cloned invertebrate ion channels, evidence in mammals? Hatton…

HISTAMINE ACTIONS IN THE CNS (LBH)

Histamine in the brain may act as both a neuromodulator and as classical transmitter.

Histaminergic neurons can regulate and be regulated by other transmitter systems.

Histamine in the central nervous system may participate in a variety of brain functions.

Histamine may contribute to brain diseases or disorders.

SIGNIFICANCE OF BRAIN HISTAMINE FOR DRUG ACTION (LBH)

Drugs which modify sleeping and waking act through the histaminergic system.

Classical H1 antagonists; H1 sedative properties of antidepressants and atypical anti-psychotics

Modafinil and wake-promoting effects

Morphine-like analgesics activate brain histaminergic mechanisms

Drugs which act on H3 receptors are being developed for treating obesity, sleep disturbances, epilepsy, pain and/ or cognitive disorders.

15. Glutamate and Aspartate

Raymond Dingledine and Bjørnar Hassel

Glutamatergic transmission and energy metabolism are interwoven.

- Neuronal TCA intermediates are diverted for synthesis of glutamate and aspartate.
- Glutamate can also be synthesized from glial glutamine: the glutamine cycle.
- Leucine and other amino acids contribute amino groups to glutamate synthesis.
- Glutamate is an important energy source for astrocytes.
- Glutamate is also important for glutathione synthesis, ammonia detoxification and protein synthesis.
- Vesicular glutamate transporters are essential for transmitter release.

Iontotropic glutamate receptors mediate fast excitatory transmission

- Five receptor families are defined by structural homology
- Receptor activation involves a clam-shell closure mechanism
- Endogenous allosteric modulators regulate synaptic transmission
- Ca entry through ionotropic receptors triggers synaptic plasticity
- Cytoplasmic proteins regulate receptor targeting
- Receptor knockouts reveal clues to function

Metabotropic glutamate receptors modulate excitatory and inhibitory transmission

- Eight mGluR are in three families
- G-proteins and other proteins mediate functional effects
- Pre- and postsynaptic mGluR's mediate synaptic plasticity

Glutamate receptor activation triggers multiple intracellular responses

Is aspartate a transmitter?

Glutamate transporters shield the brain from ischemic injury and epilepsy

- Five transporters mediate ATP-requiring uptake into neurons and glia
- Glial transporters reduce ischemic brain injury
- Neuronal transporters enhance GABAergic tone

Summary: dual roles of glutamate as information mediator and metabolic regulator

GABA and Glycine

Outline (January 2004)

Richard W. Olsen and Heinrich Betz

Basic Neurochemistry, 7th ed

Introduction (without title)

I. GABA Synthesis, Uptake and Release

- **GABA is formed in vivo by a metabolic pathway referred to as the GABA shunt**

II. GABA Receptor Physiology and Pharmacology

- **GABA receptors have been identified electrophysiologically and pharmacologically in all regions of the brain and are generally inhibitory**
- **$GABA_B$ receptors are coupled to G proteins and a variety of effectors**
- **$GABA_A$ receptors are ligand-gated chloride channels**
- **The $GABA_A$ receptor is the major molecular target for the action of many drugs in the brain**
- **Neurosteroids, which may be physiological modulators of brain activity, enhance $GABA_A$ receptor function**

III. Cloning GABA Receptors

- **$GABA_B$ receptors are heterodimers**
- **A family of pentameric $GABA_A$-receptor protein subtypes**
- **Sequencing revealed that the $GABA_A$ receptor is a member of a superfamily of ligand-gated ion channel receptors; structural models are being developed**
- **Mouse genetics reveal important functions for $GABA_A$ receptor subtypes**

IV. Glycine is synthesized from glucose and other substrates in the brain

V. Glycine Receptor Physiology and Pharmacology

- **A number of amino acids can activate, to varying degrees, the inhibitory glycine receptor**
- **Glycine inhibition is important in the spinal cord and impaired in some neurological disorders**
- **Glycine is inhibitory on ligand-gated, strychnine-sensitive Cl^- channel receptors but excitatory on N-methyl-D-aspartate receptors**

VI. Cloning Glycine Receptors

- **Glycine receptors belong to the same gene superfamily as the $GABA_A$ receptor**

VII. GABA and Glycine are the Major Rapidly Acting Inhibitory Neurotransmitters in Brain

VIII. References

17. Purinergic Systems

Joel Linden and Diane Rosin
Correspondence to Joel Linden, Cardiovascular Research Center, University of Virginia, MR5 Box 801394 Charlottesville, Virginia 22908.

Figure 17-1. Adenosine 5′-triphosphate. A purine nucleotide consisting of adenine, ribose and triphosphate.

Purine release and metabolism

Many cells in the nervous system release adenosine and adenine nucleotides
Nucleotides can be metabolized in the extracellular space
Adenosine is considered to be a neuromodulator

Figure 17-2. Purine release and metabolism.
Figure 17-3. Adenosine metabolites.
Table 17-1. Substrates and Inhibitors of Enzymes Involved in Nucleotide and Nucleoside Metabolism
Box 17-1. Inherited Diseases of Purine Metabolism

Purinergic Receptors

Adenosine also binds to an intracellular site on adenylyl cyclase
There are four subtypes of adenosine receptor that have been cloned
Xanthines block P1, but not P2, receptors
Subtypes of P2 receptors can be classified pharmacologically
Receptors exist for diadenosine polyphosphates, distinct from P1 or P2 receptors

Figure 17-4. The purinergic receptor family.
Figure 17-5. Deduced amino acid sequence and structure of the human A_1 adenosine receptor.
Figure 17-6. Dendograms illustrating structural similarities among G protein-coupled purinergic receptor subtypes.
Figure 17-7. Structures of selective agonists and antagonists of adenosine receptors.
Table 17-2. Subtypes of Adenosine Receptor, Their Effectors and Selective Agonists and Antagonists
Table 17-3. Distribution of P2 mRNAs in the CNS

Effects of Purines in the Nervous System

Adenosine receptors
- **A_1-adenosine receptors, sleep and epilepsy**
- **A_{2A}-adenosine receptors, locomotor behavior and Parkinson's disease**
- **A_{2B}-adenosine receptors**
- **A_3-adenosine receptors**

ATP receptors
- **P2X receptors**
- **P2Y receptors**
  - **$P2Y_1$ receptors**

Figure 17-8. Distribution of A_1 and A_{2A} receptors in rat brain.
Figure 17-9. Regulation of Striatal function by A_{2A} adenosine receptors

References

18. PEPTIDES

Richard E. Mains and Betty A. Eipper

The major changes/improvements are:

1. A lot more is known about the endoproteases, exoprotease, and amidating enzyme now than in 1997, with crystal structures for a couple and more on the mechanisms of how the proteases work and their selectivity.
2. Some of the methods listings will go away – while relevant in a global presentation, there is not space in such a short chapter and modern things have to hold sway over historically interesting approaches
3. There will be a discussion of the impact of genomics and proteomics on the study of peptides. Specifically, there can now be some pretty clear statements about how many families of peptides and enzymes there are, although we will also remind the readers about how (relatively) tiny the coding regions can be for many peptide precursors (as little as 276 nt or thereabouts) and with no introns, such a tiny exon could get lost in the noise of genomic sequencing. Proteomics makes its own special impact, on "what is really there" as opposed to the theoretical predictions.
4. Different receptors will be discussed entirely – the opiate receptors, orexin and ghrelin receptors are far more topical and make lovely examples. Orphan receptors have driven a number of discoveries of new peptides.
5. There has been a lot of progress in the area of synthetic peptide analogs – both agonists and antagonists – as one might expect from the classical neurotransmitter field from a couple of decades earlier.

Next page

The 1997 chapter in outline form, with ADDITIONS for 2003 IN CAPITAL LETTERS:

I. The Neuropeptides
A. Many neuropeptides were originally identified as pituitary hormones or as hormones of the gastrointestinal tract.
B. Neuropeptides far outnumber the classical neurotransmitters.
C. The use of peptides as messengers is evolutionarily very old.
D. A variety of techniques are being used to identify additional neuropeptides. quickly list bioassays; radioreceptor assays; COOH-terminal alpha-amides; classical molecular biology; GENOMIC APPROACHES; PROTEOMICS; ORPHAN RECEPTORS
E. The neuropeptides exhibit a few key differences from the classical neurotransmitters. Lower levels, inactive large precursors, synthesis must start in the soma, no synaptic re-use, role of calcium in release is different.
F. Neuropeptides are found in many neurons, and often in the same synapses with conventional neurotransmitters — EMPHASIZE PLASTICITY
G. The biosynthesis of neuropeptides is fundamentally different from the biosynthesis of conventional neurotransmitters.
H. Many of the enzymes involved in peptide biogenesis have been identified.
I. Key enzymes in neuropeptide biosynthesis -- BIG EXPANSION ON ENDOPROTEASES, CARBOXYPEPTIDASE E, AMIDATING ENZYME based on crystal structures and much more on enzymatic mechanism.
Downplay other enzymes for which there is no progress. Still use the example of POMC Processing.
J. Neuropeptides are packaged into large dense core vesicles (LDCVs).
K. Diversity is generated by families of propeptides, alternative splicing, proteolytic processing and post-translational modifications.
L. METABOLIC REGULATION; VOLUME TRANSMISSION OF PEPTIDES (as catecholamine folks are accustomed to believing) PLUS MATCHING GPCR'S WITH ACTUAL PEPTIDES (WHICH IS USUALLY NOT A GOOD MATCH).

Next page

II. Neuropeptide Receptors

A. Most neuropeptide receptors are seven transmembrane domain G protein coupled receptors. BUILD FROM THE RHODOPSIN CRYSTAL STRUCTURE TO MODELS OF PEPTIDE RECEPTORS WITH MANY SITE_DIRECTED MUTAGENESIS STUDIES.

B. Neuropeptide receptors are not confined to synaptic regions and the expression of peptide receptors and the corresponding peptides are not well matched.

C. The amiloride-sensitive FMRF-amide gated sodium channel was the first peptide gated ion channel identified. STILL THE ONLY EXAMPLE(?)

D. PEPTIDE ANALOGS AS A KEY TOOL IN THE STUDY OF PEPTIDE ACTIONS AND RECEPTORS

E. AGOUTI-RELATED PEPTIDE AS EXAMPLE OF ENDOGENOUS ANTAGONISTS

F. MCR1,2,3,4,5 AS EXAMPLES OF RECEPTORS RELATED TO PEPTIDE DIVERSITY

G. KNOCKOUTS OF PEPTIDE VS. PEPTIDE RECEPTORS – UNLIKE THE GROWTH FACTOR FIELD WHERE RECEPTOR KO'S ARE WORSE THAN PEPTIDE KO'S, IN THE PEPTIDE FIELD, THE PEPTIDE KO'S ARE THE KEY THING.

III. Neuropeptide Functions

A. The study of peptidergic neurons requires a number of special tools.

- Antibody-based
- RNA-based
- Direct methods
- Peptide agonists and antagonists
- Ligand binding assays
- PCR-BASED DIFFERENTIAL EXPRESSION
- GENOMICS TO PREDICT PEPTIDE PRECURSORS
- PROTEOMICS AT THE SINGLE CELL OR SMALL TISSUE SAMPLE LEVEL

B. Plurichemical coding of neuronal signals. Peptides along with conventional neurotransmitters.

C. Neuropeptides make a unique contribution to signaling. BRIEF!

D. Regulation of neuropeptide expression is exerted at several levels. MORE HERE – HOMEOBOX and MASTER TRANSCRIPTIONAL FACTORS NEED TO BE INCLUDED.

E. T-PIT HERE

Next page

IV. Peptidergic Systems In Disease

A. Diabetes insipidus IS PERHAPS A LESS INTERESTING EXAMPLE THAN OBESITY AND BEHAVIORAL CASES – EXCEPT DOMINANT-NEHATIVE MUTANTS MAKE THIS COOL.

B. In fat/fat mice, a mutation in the CPE gene causes late onset diabetes with hyperproinsulinemia – STILL INTERESTING AND STILL NOT REALLY UNDERSTOOD.

C. Obesity can have several central nervous system components involving CCK, leptin, and NPY. MANY MORE PEPTIDES CAN BE INCLUDED HERE – BECOMES AN UNINTERPRETABLE LIST, HOWEVER, SO THIS HAS TO BE LIMITED IN SCOPE AND CAREFULLY ORGANIZED

D. CCK agonists and antagonists are yielding insights into the neurochemical basis of panic attacks and satiety – PROGRESS HAS OCCURRED BUT MAYBE NOT ENOUGH TO KEEP THIS SECTION.

E. Enkephalin knock-out mice reach adulthood and are healthy, fertile and care for their young – ALSO NOT AS INTERESTING IN 2003.

F. MIGRAINE HEADACHES DUE TO CGRP ARE VERY TOPICAL NOW – SHOULD INCLUDE.

G. OREXINS AND NARCOLEPSY OR OVER-EATING OR BOTH.

H. GHRELIN – INTERESTING ADDITIONAL POST-TRANSLATIONAL MODIFICATIONS OF PEPTIDES, AND FASCINATING RAPID PROGRESS IN UNDERSTANDING ANOTHER APPORACH TO OVER-EATING

FIGURES WILL CHANGE WITH THE TOPICS

1. Selected bioactive peptides, grouped by structural similarity or by tissue source.
2. Structures of selected bioactive peptide precursors.
3. Intracellular pathway of bioactive peptide biosynthesis, processing, and storage.
4. Tissue specific processing of the proopiomelanocortin precursor yields a wide array of bioactive peptide products.
5. Sequential enzymatic steps lead from the peptide precursor to bioactive peptides.
6. Processing of the proopiomelanocortin precursor proceeds in an ordered, stepwise fashion.
7. Cell-specific packaging of peptides into LDCVs can lead to very different patterns of peptide secretion.
8. MECHANISMS OF THE ENDOPROTEASES/CARBOXYPEPTIDASE/AMIDATING ENZYME. CONNECT STRUCTURES AND ENZYMATIC MECHANISMS.
9. Serpentine (7 transmembrane domain) receptors for peptides have binding regions within the membrane and in the NH_2-terminal loop. BUILD FROM RHODOPSIN AND USE SITE-DIRECTED MUTANTS
10. Plurichemical transmission —WILL AIM AT A MORE INTERESTING EXAMPLE, NOT CLEAR WHICH EXAMPLE YET.
11. Regulation of neuropeptide expression is exerted at several levels.
12. MULTIPLE ACTIONS OF PEPTIDES – OREXINS; MSH; CCK; ACTH. IDEA IS TO LIST ABOUT 5 PEPTIDES WITH “CLASSICAL” ACTIONS AND TARGETS, PLUS “NEW” ACTIONS AND TARGETS.

19. G Proteins

Eric J. Nestler and Ronald S. Duman

20. PHOSPHOINOSITIDES

Anne M. Heacock and Stephen K. Fisher

21. Cyclic Nucleotides

Ronald S. Duman and Eric J. Nestler

23. Serine and Threonine Phosphorylation

James A. Bibb and Eric J. Nestler

22. Calcium

Gary Bird and James Putney Jr.

The Concept of Ca^{2+} as a Cellular Signal

Measurement of Cellular Ca2+ Concentrations and Movements

Ca^{2+} Regulation at the Plasma Membrane

Two distinct mechanisms for controlling [Ca^{2+}] at the plasma membrane are a Ca^{2+}-ATPase pump and a Na^{+}- Ca^{2+} exchanger.

Ca^{2+} Stores and Ca^{2+} Pools

The only known mechanism for accumulation of Ca^{2+} by the endoplasmic reticulum is through the actions of SERCA pumps.

Mitochondria may accumulate Ca^{2+} by an energy-dependent process

Calcium is stored at other significant sites in the cell.

Ca^{2+} Signaling

Release of intracellular Ca^{2+} is mediated primarily via inositol 1,4,5-trisphosphate receptors and ryanodine receptors.

Ca2+ enters cells either via voltage-dependent or voltage-independent channels.

Periodic temporal and spatial patterns of Ca^{2+} signaling give rise to calcium oscillations and waves.

Although distinct, Ca^{2+}-signaling events in excitable and nonexcitable cells share some common characteristics.

Ca^{2+}-Regulated Processes

Ca^{2+} is required for acute cellular responses, such as contraction or secretion.

Ca^{2+} also plays a role in more prolonged cellular events, such as mitogenesis and apoptosis.

References

24. Tyrosine phosphorylation

Lit-fui Lau and Richard L. Huganir

1. Tyrosine phosphorylation in the nervous system—General Introduction

2. Protein tyrosine kinases
    a. Nonreceptor protein tyrosine kinases
        i. Unique domain
        ii. SH3
        iii. SH2
        iv. SH1
        v. Regulation of kinase activities
    b. Receptor protein tyrosine kinases
        i. Extracellular domain
        ii. Transmembrane domain
        iii. Cytoplasmic domain
        iv. Regulation of kinase activities

3. Protein tyrosine phosphatases
    a. Nonreceptor protein tyrosine phosphatases
    b. Receptor protein tyrosine phosphatases

4. Tyrosine phosphorylated substrates
    a. Ligand-gated ion channels
        i. Acetylcholine receptor
        ii. NMDA receptor
        iii. GABA receptor
    b. Voltage-gated ion channels
        i. potassium channels
        ii. sodium channels
        iii. voltage-gated cationic channel

5. Role of tyrosine phosphorylation in the nervous system
    a. Survival and differentiation
    b. Axonal guidance
    c. Synapse formation and plasticity
        i. Neuromuscular junction
            1. agrin
            2. ARIA
        ii. Central synapses
            1. ephrinB-ephB
            2. BDNF
    d. Neurological disorders

26. Transcription

Jim Eberwine

27. GROWTH FACTORS

Gary Landreth *gel2@po.cwru.edu*

GROWTH FACTORS ARE ESSENTIAL FOR NERVOUS SYSTEM DEVELOPMENT AND FUNCTION

1. Growth factors are proteins that stimulate cellular proliferation and promote cellular survival.

2. Growth factors activate multiple signal transduction pathways required for survival and differentiation.

3. Growth factors activate multiple signal transduction pathways required for survival and differentiation.

CLASSES OF GROWTH FACTORS ACTING IN THE NERVOUS SYSTEM

1. The neurotrophins comprise a family of highly related molecules which act to support the survival and phenotypic specificity of select subsets of neurons.

Nerve Growth Factor.
Brain-Derived Neurotrophic Factor
Neurotrophin 3
Neurotrophin 4/5

Neurotrophins, synaptic plasticity and neurotransmission

2. Neurotrophic Cytokines are a small group of cytokine-like molecules that act in the nervous system.

Ciliary Neurotrophic Factor
Leukemia Inhibitory Factor
Interleukin 6
Cardiotrophin 1
Other Cytokines

3. The fibroblast growth factors comprise a gene family of nine members which share substantial sequence homology and have diverse effects in the nervous system.

- next page -

4. Transforming growth factors b are the prototypic members of a large family of related factors which have a diverse roles both in development and in the mature animal.
    TGFß subfamily
    Bone Morphogenetic Protein Subfamily

5. Glial-Derived Neurotrophic Factor family represents a newly recognized family of target-derived neurotrophic factors.
    Glial-Derived Neurotrophic Factor
    Neurturin
    Artemin
    Persephin

6. Epidermal Growth Factor and related factors have a diverse range of actions in the nervous system.
    Epidermal Growth Factor and TGFa
    Neuregulins

7. A number of other growth factors act in the nervous system:
    Platelet-Derived Growth Factor
    Insulin-Like Growth Factor I
    Hepatocyte growth factor
    Macrophage stimulating factor

GROWTH FACTORS ACT COMBINATORIALLY AND SEQUENTIALLY TO REGULATE NERVOUS SYSTEM DEVELOPMENT

References
Tables-1 and 2
Figure 1-4

29. Stem Cells

Outline for Basic Neurochemistry: 6/18/03

Alison K. Hall

1) There are different types of stem cells
    i) Stem cell is multipotent and self renewing
    ii) Embryonic stem cells are origin of all cells
    iii) Fetal stem cells build tissues
    iv) Adult stem cell replenish tissues
        (a) Hematopoietic, mesenchymal, neural
        (b) Concept of cell fate restriction

2) Lessons from the hematopoietic stem cell
    i) Reconstitutes all cells in blood
    ii) Few stem cells present in bone marrow, peripheral blood
    iii) Growth factors regulate survival, amplification of stochastically generated cells

3) Stem cells contribute to the developing nervous system
    i) Neural crest stem cell
    (1) Environmental cues determine cell fate
        (a) Different from hematopoietic stem cells
        (b) Concept of induction, instructive cues
    (2) Role of intrinsic transcription factors
    ii) CNS stem cells (eg Jessell)

4) Neural stem cells offer potential for repair in the adult nervous system.
    i) Neurons postmitotic, neurodegeneration results in cell, functional loss
    ii) Fetal neural stem cells for therapy
        (a) Stem cells can be propagated as neurospheres
    iii) Adult neural stem cells for therapy
    iv) The developmental biology: is this selection or instruction?
    v) Insert Box example: Promise for Parkinson's?

5) Brain cells can be derived from non-brain stem cells
    i) In vitro/in vivo issue?
    ii) Bone marrow stem cell therapy for leukodystrophy
    iii) Concept of injury signals that guide homing

`

6) Common stem cell therapy challenges
    i) Sufficient number of single population
    ii) Effective connectivity, survival, function
    iii) Ethical issues
    iv) Tumor formation?

30. Axonal Growth in the Adult Nervous System

Wendy.Kartje and Martin Schwab

I. Background:

a) CNS and PNS axonal regeneration; increased after PNS injury, limited after CNS injury.

II. Regeneration in the PNS after lesion:

a) Remodeling of the nerve-muscle endplate in normal and d. muscle (role of activity in shaping circuitry).
b) Injury to peripheral nerve:
    1. Wallerian degeneration, schwann cells and glial cells remove myelin/schwann cells go back to early developmental stages/increase in trophic factors, ECM factors
    2. Proximal nerve stump: sprouting and elongation/ cell bodies increase growth associated proteins, ie GAP-43, others.
    3. Crush injury: basement membrane stays intact, good regeneration and pathfinding vs nerve cut, with scar, worse pathfinding.
    4. Recovery of function: animal models vs. clinical/crush vs. cut (aberrant connections)

III. CNS injuries:

a) Stroke, traumatic head injuries/loss of nerve cell bodies
    1. Transplants, stem cells as cellular replacements/not very successful
    2. Compensatory sprouting of spared neurons/probably underlying spontaneous (but limited) recovery of function.
b) SCI (trauma,bleeding,MS-plaques)/ axonal tract lesions
    1. Distal to lesion: Wallerian degeneration (by microglia/macros):slow
    2. proximal stump sprouting/limited: 4 possible reasons:
        i.) adult neurons do not grow well although there is spontaneous increase of GAP-43, Aguayo experiments, ie growth response of CNS neurons to lesions can be enhanced, GAP/CAP (Caroni-Skene)/Inosine (Benowitz)/Trophic factors
        ii.) Inhibitors, especially in myelin, ie Nogo, MAG, etc in-vitro studies/ IN-1, anti-Nogo antibodies in-vivo application leading to regeneration, anatomical plasticity and functional recovery.
        iii.) Inhibitors in scars, CS-PGS (Silver-Fawcett)
        iv.) Insufficient trophic support, trophic factors in SCI, ie NT-3 (Tetzlaff, etc).

IV. Two ways to functional recovery: regeneration and compensatory neurite growth

a) Target finding, specific synapse formation
    1. guidance factors: present in adult nervous system but function not know.
    2. activity-dependent stabilization

b) Partial lesions to long tracts frequent/or parallel tract systems/spared fibers take over targets by compensatory sprouting.

31. Energy Metabolism of the Brain

Mary McKenna, Rolf Gruetter, Ursula Sonnewald and Arne Schousboe

first draft of outline 7/03

Introduction

- The brain consumes about one-fifth of total body oxygen utilization
- The main energy-demanding functions of the brain are those of ion flux related to excitation and conduction
- Brain metabolism is complex-- Neurons and glia are partners in brain function

Substrates of Cerebral Metabolism

- Substrates enter the brain from the blood
- The blood-brain barrier has specific transporters for the uptake of nutrients including glucose
  - Transporters for glucose and monocarboxylic acids are developmentally regulated
- Metabolism and substrate utlilzation changes during development
- ketone bodies and lactate are important substrates for energy and synthesis of lipids and amino acids in developing brain
  - glucose is also needed by developing brain
- glucose utilization is obligatory for adult brain

Age and Development Influence Cerebral Energy metabolism

- The rate and pathways of metabolism change during development
  - Metabolic rate increases during early development
  - Metabolic rate declines and plateaus after maturation
    - Tissue pathology, but not ageing, produces secondary changes in metabolic rate

Regulation of Cerebral Metabolic Rate

- Continuous cerebral circulation is absolutely required to provide sufficient oxygen
- Cerebral metabolic rate differs regionally

Next page

Intermediary Metabolism

- Compartmentation greatly influences metabolism
- **Figure** of compartmentation
  -- several important enzymes are found only in astrocytes, e.g. pyruvate carboxylase and glutamine synthetase
  -- transporters for glucose and monocarboxylic acids are differentially distributed on brain cells (**Figure *of distribution of glucose and MCT transporters -- from Vannucci and Simpson if possible)***
  -- glutamate in brain is compartmented into separate pools
  -- Glycogen is a dynamic but limited energy store localized in astrocytes in brain glycogen is broken down to lactate, not glucose

- There is a continuous dynamic exchange of compounds neurons and glial cells called "metabolic trafficking"
  - Glutamate from neurons is converted to glutamine by astrocytes and released
  - Uptake of neurotransmitters influences astrocyte metabolism

- ATP production in brain is highly regulated
  - Brain glycolysis is regulated mainly by hexokinase and phosphofructokinase
  - The pyruvate dehydrogenase complex plays a key role in regulating oxidation
  - Energy output and oxygen consumption are associated with high rates of enzyme activity in the Krebs cycle
  - Substrates other than glucose provide energy for brain cells (e.g. glutamate, glutamine, lactate, fatty acids, ketone bodies)

- The malate/aspartate shuttle has a key role in brain metabolism
  - Essential for transferring reducing equivalents from the cytosol to the mitochondria
  - Links energy metabolism and neurotransmitter biosynthesis

- The pentose shunt, also termed hexose monophosphate pathway, is active in brain
  - The NADPH produced by this pathway is important for lipid biosynthesis and maintaining reduced glutathione

- The pyruvate recycling pathway can maintain TCA cycle activity when glucose is low

- Mitochondrial heterogeneity—many enzymes and components of oxidative phosphorylation are differentially distributed in neuronal and glial mitochondria

- Current controversies -- mention Lac shuttle – [where to put this??]

Next page

How Brain Metabolism is Studied

- **In Vivo** – Many techniques can be used to study or determine brain metabolism in vivo
  - Clinical and research -- cerebral metabolic rate is determined locally by functional activity in discrete regions
    - Oxygen utilization in the cortex is measured by polarographic techniques
    - PET scanning measures regional uptake of glucose and other substrates by brain
    - NMR spectroscopy is an important tool for studying brain metabolism
      - fMRI is used to study regional metabolism
      - ^{31}P-NMR is used to determine ATP and high energy phosphates
      - ^{13}C-NMR is used to determine pathways of substrate metabolism and neuronal/glial trafficking
  - Primarily research
    - microdialysis and microelectrodes are used to determine the concentration of compounds in the extracellular space in brain

  - Damaged or abnormal areas of brain exhibit altered metabolism

- **In Vitro –** in vitro studies are not complicated by blood flow and hormonal influences
  - Preparations
    - Primary cultures of brain cells are an important tool for studying differences in metabolism of neurons and glia
    - Brain slices and cocultures are used to study metabolism and neuronal/glial interactions
    - Isolated mitochondria are used for enzyme and metabolic studies
    - Autoradiography is used to study regional uptake of substrates
- NMR spectroscopy has led to major advances in our understanding of brain metabolism

Cerebral Energy Metabolism in Physiological and Pathological States

- Normal metabolism depends on circulation for oxygen and glucose
  - blood and cerebral spinal fluid chemical changes can alter metabolism
- Anesthesia, coma and systemic metabolic disease depress brain metabolism
- Damaged or abnormal areas of brain exhibit altered metabolism in vivo and in vitro
- Alterations in energy metabolism can be due to changes in neurons, changes in glia, alterations in neuronal/glial trafficking
- Compromised energy metabolism can result in neurodegeneration

Next page

Tentative Figures (not final or complete)

1—schematic of neuronal/glial trafficking
2--figure of distribution of glucose and MCT transporters on BBB and brain cells
3--Metabolism -- glycolysis, TCA cycle
4--compartmentation of metabolism (could be combined with 1)
5--^{31}P-NMR spectra of high energy metabolites (source? Can we get permission for literature figures?)
6a & 6b --^{13}C-NMR spectra of whole brain [acetate and glucose; separate or together?] & labeling pattern figure
7a & 7b—^{13}C-NMR spectra of brain cells [media and PCA extract separately—either astrocytes or neurons]

Tables (not final or complete)

Table 31-1 Cerebral Blood Flow and metabolic rate in a normal young adult man (possibly keep)
1--Table of rates of regional glucose utilization (to show differences)
2--Table of rates metabolism of substrates by brain cells [lit data; Edmond, McKenna, Schousboe, etc)
3--Table showing neuronal vs glial distribution of electron transport chain components (from John Clark's work)
4--Table of compounds labeled in NMR spectra of brain (to go with spectra in 6a)
5-- Table of compounds labeled in NMR spectra of brain cells (to go with spectra in 7a & b)
Table 31-6. Cerebral Blood Flow and Oxygen Consumption in Human from Childhood to Old Age and Senility (possibly keep and update if needed)

Questions

Do we need a PET, of FMRI image or will imaging chapter take care of those?
How much of blood flow will be encompassed in the imaging chapter?

How much to say about currently controversial areas e.g. ANSLH

Things in current chapter that will be deleted: (tentative)

Table 31-2 Representative values for local cerebral glucose utilization in the normal conscious albino rat and monkey (umol/100g/min)
Table 31-3. Relationship Between cerebral oxygen consumption and glucose utilization in a normal young adult man
Table 31-4. Effects of Insulin hypoglycemia on cerebral circulation and metabolism in humans
Table 31-5. Effectiveness of various substances in preventing or reversing the effects of hypoglycemia or glucose deprivation on cerebral function and metabolism
Table 31-7. Relationship Between Level of Consciousness and Cerebral MetabolicRate
Table 31-8. Cerebral Blood flow and metabolic rate in schizophrenia and in normal young men during LSD-induced psychotomimetic state

Figure 31-1. Glycogen metabolism
Figure 31-2. Glycolysis in brain
Figure 31-3. Theoretical basis of
Figure 31-4. Autoradiograms of coronal
Figure 31-5. Local glucose utilization
Figure 31-6. Effects of Electrical

32: Hypoxic-Ischemic Brain Injury and Oxidative Stress

Laura L. Dugan *duganl@neuro.wustl.edu*

Introduction

Hypoxia-ischemia and brain infarction.

1 Rapid energy failure causes disruption of ionic homeostasis and accumulation of extracellular neurotransmitters.

2. Focal and global ischemia produce different distributions of injury.

3. The "selective vulnerability" of specific populations of neurons or glial cells is not explained by vascular distribution.

Microvascular injury in hypoxia-ischemia

1. Hypoxia-ischemia disrupts the blood-brain barrier and damages endothelial cells.

2. Metalloproteinases may be involved in cerebrovascular injury

3. Consequent edema and secondary ischemia can produce further brain damage.

4. Role of aqueporins in brain edema

Excitotoxic injury in hypoxia-ischemia

1. Both NMDA and AMPA/kainate receptors contribute to excitotoxic degeneration of neurons and glia.

2. Excitotoxicity leads to increased intracellular Ca^{2+} and Zn^{2+}, which can activate toxic intracellular pathways.

Ischemic Apoptosis

1. Hypoxia-ischemia may initiate apoptosis in parallel with excitotoxicity.

2. Triggers of ischemic apoptosis may include decreased supply or sensitivity to neurotrophins, oxidative stress, or exposure to inflammatory cytokines.

Reactive oxygen and nitrogen species in hypoxia-ischemia

1. Reactive oxygen species (ROS) and nitrogen species (RNS) are required intermediates in many biological reactions, but may damage macromolecules

2. ROS/RNS generated during ischemia-reperfusion injury contribute to injury and may compromise brain metabolism

3. Brain antioxidant defenses modify ischemia-reperfusion injury.

Neuroprotective strategies for hypoxic-ischemic injury

1. Endogenous protective programs may include ischemic preconditioning and the heat shock response

2. Efficacy of thrombolytics and neuroprotective drugs in hypoxia-ischemia

33. Lipid messengers in cell function and diseases

Nicolas G. Bazan

1. Introduction

A. ***Develop the concept that synaptic membranes as well as other cell membranes (in neurons, astrocytes, brain microvasculature,/infiltrating inflammatory cells, etc) contain specific phospholipids that are reservoirs of lipid messengers.***

B. Specific signals (e.g., neurotransmitters , neurotrophic factors) activate enzymes that cleave the reservoirs releasing the messengers.

C. Remodeling of polyunsaturated fatty acyl chains in membrane phospholipids. Signaling through lipid messengers that regulate cell functions and the overactivation of some of these events in pathological conditions.

2. Phospholipases A2

A. cPLA2

B. sPLA2

a. Multiple isoforms

b. The enzyme an intercellular messenger by itself

C. iPLA2

3. Phospholipase C

4. Phospholipase D

5. Diacylglycerol- and monoacylglycerol- lipases

6. Diacylglycerol kinases

A. Multiple isoformes

B. Brain specific diacylglycerol kinase epsilon

7. Cyclooxygenases and lipoxigenases

8. Arachidonic acid

go to next page

9. Synaptic activation, ischemia or seizures stimulate phospholipases

A. The accumulation of arachidonic, docosahexaenoic and of other fatty acids.
B. Diacylglycerol release

10. Eicosanoids

A. Prostaglandins and related bioactive lipids
B. Lipoxygenase messengers
C. Lipoxins
D. Leukotrienes
E. Epoxi- and hydroxyl-modified arachidonIc acids

11. Cyclooxygenase 2-generated prostaglandin E2 modulates postsynaptic membrane excitability and long -term synaptic plasticity.

A. Prostaglandins synthesis and release from astrocytes
B. Prostaglandins synthesis and release from neurons

12. Ischemia-reperfusion and proinflammatory pathologies promote the accumulation of oxygenated lipid messengers as well as of lipid peroxidation products.

13. Endocannabinoids

A. Anandamide (N-arachidonoylethanolamine)
B. 2-arachidonoyl-glycerol, 2-arachidonoyl-glyceryl ether and virodhamine.
C. Cannabinoid receptors

14. Docosahexaenoic acid ***Develop the theme that docosahexaenoic acid, derived from the essential fatty acid linoleic acid, is the only polyunsaturated exclusively concentrated in the central nervous system.***

A. Synaptic membranes
B. Photoreceptors
C. The liver supply of essential fatty acids to the brain and retina; transport, uptake and retention
D. Significance in retinal degenerations
E. Enzyme-mediated synthesis of docosanoids
   a. Docosanoids in brain ischemia-reperfusion
   b. Docosanoids and leukocyte infiltration in experimental stroke
   c. Docosanoids and proinflammatory gene expression
   d. Significance of docosahexaenoic acid in experimental stroke and neuroprotection
F. Peroxidation and oxidative stress
G. Neuroprostanes

go to next page

34. METABOLIC ENCEPHALOPATHIES

Roger F. Butterworth

INTRODUCTION

ELECTROLYTE IMBALANCE

- Hyponatremia
- Central pontine myelinolysis is an iatrogenic disorder caused by too rapid correction of hyponatremia
- Hypernatremia

VITAMIN DEFICIENCIES

- Thiamine deficiency (Wernicke-Korsakoff syndrome)
- The "biochemical" (reversible) lesion in thiamine deficiency results from the consequences of decreased brain pyruvate oxidation.
- The thiamine-dependent enzyme α-ketoglutarate dehydrogenase is sensitive to oxidative stress
- Pyridoxine deficiency
- Folate/vitamin B_{12} deficiency
- Nicotine acid deficiency

METABOLIC ENCEPHALOPATHIES DUE TO SYSTEMIC DISEASE

- HEPATIC ENCEPHALOPATHY
    - Liver failure leads to the accumulation of toxic substances (ammonia, manganese) in the brain
    - Hepatic encephalopathy is a disorder of multiple neurotransmitters

- UREMIC/DIALYSIS ENCEPHALOPATHIES
    - Uremia results in alterations of the blood brain barrier
    - Aluminium neurotoxicity plays a role in the pathogenesis of dialysis encephalopathy

- DIABETIC/INSULIN COMA

REFERENCES

35. Apoptosis and Necrosis

Mark P. Mattson and Nicolas Bazan
mattsonm@grc.nia.nih.gov nbazan@lsumc.edu

36. NEUROPATHY

David Pleasure

Introduction:

peripheral nervous system anatomy;

clinical, electrophysiological, pathological classification of neuropathies;

special anatomic and molecular vulnerabilities of peripheral nerve.

Body of chapter *(each section to emphasize molecular mechanisms in so far as possible)*

toxic neuropathies: metals, organophosphates, medications, etc.

metabolic neuropathies: thiamine deficiency, diabetic.

genetic neuropathies: CMT, amyloids, mitochondrial.

infectious neuropathies: leprosy, HIV, Lyme, syphilis, etc.

immunologically mediated neuropathies:
Guillain-Barre, axonal Guillain-Barre, paraneoplastic, arteritic.

enteric neuropathies: Chagas, Hirschsprungís, etc.

Mechanisms of nerve regeneration and therapeutic approaches to neuropathy.

Summary

Bibliography

38. DISEASES INVOLVING MYELIN

Richard H. Quarles, Pierre Morell and Henry McFarland

(This outline is based on the 6th Edition. Items shown in [square brackets] below indicate subtopics that were covered, but not in the published outline. Changes planned for the new edition are shown in ***bolded blue italics***.)

I. GENERAL CLASSIFICATION

A. A deficiency of myelin can result either from failure to produce the normal amount of myelin during development [hypomyelination or dysmyelination] or from myelin breakdown after it is formed [demyelination].

B. Many of the biochemical changes associated with myelin deficiency are similar regardless of etiology.

II. ACQUIRED DISORDERS OF MYELIN HAVING AN ALLERGIC AND/OR INFECTIOUS BASIS

A. Nervous system damage in many acquired allergic and infectious demyelinating diseases is directed specifically against myelin or myelin-forming cells. ***(Because of the increased attention to axonal injury in many of these disorders including MS, this section needs to be changed with discussion of axonal pathology resulting either from inflammation or loss of the influence of myelin sheaths exerted by molecules such as PLP, MAG, CNPase, etc. Coordination with chapters #4 (myelin formation etc.) #8 (cytoskeleton) and the new #30 (axonal growth and regeneration) will be important here.)***

B. Experimental allergic encephalomyelitis (EAE) is an animal model of autoimmune demyelination [general aspects; acute and chronic forms; MBP, PLP and MOG as immunogens; pathogenic mechanisms; treatment]. ***(More discussion of MOG-induced relapsing/remitting EAE as a good model of MS).***

C. A number of disorders in animals caused by viruses involve primary demyelination and often are associated with inflammation. [Canine distemper virus; visna; mouse hepatitis virus; Theiler's virus].

D. Multiple sclerosis (MS) is the most common demyelinating disease of the CNS in humans. [General clinical and pathological aspects; imaging; biochemical analyses of lesions; genetics; epidemiology; evidence for viral and/or autoimmune etiology; therapy*]* ***(Increased discussion of MS subtypes with myelin or oligodendrocytes as the primary target; HHV6 and Chlamydia pneumoniae as new candidates for infectious agents; greater emphasis on axonal injury being responsible for irreversible neurological impairment and a target for therapy)***

Fig. 1. Coronal slice of brain from a patient who died of MS

Fig. 2. Polyacrylamide gel electrophoresis of proteins in MS and control tissue

E. Some human peripheral neuropathies involving myelin are thought to be immune-mediated. [Guillain-Barre Syndrome (GBS), chronic inflammatory demyelinating neuropathy (CIDP), multifocal motor neuropathy (MMN), and neuropathy in association with IgM gammopathy; glycolipids and MAG as potential target antigens; molecular mimicry between Campylobacter jejuni and gangliosides**]** ***(increased understanding of pathogenic mechanisms based on progress with animal models and in vitro systems)***

Fig. 3. Molecular mimicry in subsets of patients with Guillain-Barré syndrome.

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F. Other acquired disorders affecting myelin in humans may be secondary to viral infections, neoplasias or immunosuppressive therapy [postinfectious encephalitis; neuroAIDS; progressive multifocal leukoencephalopathy]

III. GENETICALLY DETERMINED DISORDERS OF MYELIN

A. Spontaneous mutations in experimental animals provide insights about the structure and assembly of myelin [Mutations in proteins of compact myelin- Shiverer, jimpy, trembler; Other mutations - quaking, taiep] ***(update with important progress on pathogenic mechanisms involved)***

B. The human leukodystrophies are inherited disorders affecting central nervous system white matter. ***(update with important progress on pathogenic mechanisms; add childhood ataxia with CNS hypomyelination (CACH)/vanishing white matter (VWM) disease; add occurrence of peripheral neuropathy with some PLP mutations)***

Table 1 - Genetically determined disorders affecting CNS myelin in humans [Krabbe's disease; metachromatic leukodystrophy; adrenoleukodystrophy; Canavan's disease; Pelizaeus-Merzbacher disease; phenylketonuria]

Table 2 - Human myelin composition in three diseases compared with controls ***(probably delete and mention important aspects in text)***

C. The deficiencies of peripheral nerve myelin in several inherited neuropathies are caused by genetic mutations of sheath proteins [PMP-22, P0 glycoprotein, connexin-32]. ***(update with important progress on pathogenic mechanisms; discuss axonal pathology; add new mutations such as periaxin gene)***

IV. TOXIC AND NUTRITIONAL DISORDERS OF MYELIN ***(Shorten with combining of subheadings A and B; also delete some items and refer to earlier editions or other references)***

A. Biological toxins can produce myelin loss. [diphtheria toxin, cytokines]

B. Many chemical toxins can impair myelin formation or cause its breakdown [organotin, hexachlorophene, lead, tellurium].

C. General undernourishment or dietary deficiencies of specific substances can lead to a preferential reduction in myelin formation. [underfeeding, deficiencies of protein, essential fatty acids, vitamins and copper]

V. DISORDERS PRIMARILY AFFECTING NEURONS WITH SECONDARY INVOLVEMENT OF MYELIN ***(shorten with elimination of subheadings A and B)***

A. The archetypical model for secondary demyelination is Wallerian degeneration.

B. Secondary demyelination occurs in subacute sclerosing panencephalits (SSPE) and other diseases of the central nervous system.

VI. REMYELINATION ***(change heading to "Repair in Demyelinating Diseases" and include subheading on potential importance of axonal survival and/or regeneration)***

A. The capacity for remyelination is much greater in the PNS than the CNS.

B. Remyelination in the CNS can be promoted by various treatments, and therapy of human myelin disorders by this approach may be feasible [growth factors, transplants of myelin-forming cells] ***(Add stem cells, overcoming Notch pathway inhibition of remyelination, and enhancement of remyelination with autoantibodies)***

REFERENCES

Chapter 39:

Genetics of Neurodegenerative Diseases

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39. Genetics of Neurodegenerative Diseases

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40. Inborn Errors of Metabolism and the CNS

Marc Yudkoff and Hugo Moser

1. Introduction
    A. History of the Inborn Errors of Metabolism
        i. Garrod: Concept of an Inborn Error of Metabolism
        ii. Concept of dynamic metabolic pathway, not a static system
        iii. Relationship to developments in genetics
        iv. Development of chromatographic approaches
        v. Advent of diet-therapy and newborn screening: spurs to the field

    B. Tabular Presentation of Inborn Errors of Intermediary Metabolism
        - Disorders of Carbohydrate Metabolism
        - Aminoacidurias
        - Organic acidurias
        - Mitochondropathies
        - Disorders of purine and pyrimidine metabolism
        - Disorders of lipid metabolism
        - Peroxisomal disease
        - Lysosomal disease
        - Disorders of membrane transport
        - Disorders of porphyrin metabolism
        - Disorders of metal metabolism

II. Phenylketonuria as Exemplar of Inborn Error of Metabolism Causing Brain Damage
    A. History of PKU
    B. Gene Defect in PKU
    C. Consequences of the defect: the clinical picture in PKU
        - Relationship to IQ
        - Relationship to behavior
        - Neurocognitive profile
        - Maternal PKU
    D. PKU and brain chemistry: the major theories to explain the encephalopathy
        - Possible tyrosine deficiency
        - Impaired transport into brain of neutral amino acids
        - Deficiency of dopamine and serotonin
        - Dysmyelination
        - Impairment of cholesterol synthesis
        - Relationship to energy metabolism
    E. Implications of Theory for Therapy
    F. Future research directions

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III. Peroxisomal Disease

1. Brief review of peroxisome structrure and function
2. Peroxisome import mechanisms
3. Disorders of peroxisome biogenesis that present woth the " Zellweger, neonatal adrenoleukodstrophy, infantile Refsem Disease contimuum phenotype' . a chart of the el;even gene defects that may lead to it and genotype-phenotype correlations. Pathogenesis of neuronal migtrtion defects
4. Pex 7 deficiency and rhizomelic chondrodysplasia punctata; pathpgenesis of skeletal defects
5 Single enzyme defects that involve peroxisomal fatty acid beta osidation
6. X-linked adrenioleukodystrophy
7. Refsum disease (Phytanoyl Co-A hydoxylase deficiency)
8 Future directions

IV. Lysosomal Disease

[to be added]

42. DISORDERS OF MUSCLE EXCITABILITY

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ORGANIZATION OF THE NEUROMUSCULAR JUNCTION

Nerve and muscle communicate through neuromuscular junctions

Figure 42.1 The neuromuscular junction (photomicrograph)

Acetylcholine acts as a chemical relay between the electrical potentials of nerve and muscle

Figure 42.2 Molecular physiology of neuromuscular transmission (cartoon)

The fidelity of signal transmission relies on the orchestration of innumerable stochastic molecular events

EXCITATION AND CONTRACTION OF THE MUSCLE FIBER

The excitable apparatus of muscle is composed of membranous compartments

Figure 42.3 Organization of a skeletal myocyte (use 6th edition Figure 43.5, with modifications)

Myofibrils are designed and positioned to produce movement and force

Calcium couples muscle membrane excitation to filament contraction

Figure 42.4 Molecular physiology of muscle excitation-contraction coupling (schematic)

Table 42.1 Disorders of muscle excitability

GENETIC DISORDERS OF THE NEUROMUSCULAR JUNCTION

Congenital myasthenic syndromes impair the operation of the acetylcholine receptor

ChAT deficiency

AChR deficiency

Figure 42.5 Molecular pathology acetylcholine receptor (cartoon)

Rapsyn deficiency

Slow channel syndrome

Fast channel syndrome

Cholinesterase deficiency

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HEREDITARY DISEASES OF MUSCLE MEMBRANES

Figure 42.6 Molecular pathology of muscle voltage-gated ion channels and pumps (cartoon)

Mutations of the sodium channel cause hyperkalemic periodic paralysis

Hypokalemic periodic paralysis is due to calcium channel mutations

Abnormal potassium channels in Andersen syndrome cause more than periodic paralysis

Mutant chloride channels are responsible for myotonic dystrophy, a multisystemic disorder

Paramyotonia congenita and mutations in the sodium channel

Malignant hyperthermia caused by mutant RyR calcium release channels

Calcium channel mutations may also cause malignant hyperthermia

Brody disease is an unusual disorder of the sarcoplasmic reticulum calcium ATPase

IMMUNE DISEASES OF MUSCLE EXCITABILITY

Myastenia gravis is caused by antibodies that promote premature AChR degradation

Figure 42.7 Muscle action potentials during repetitive neural stimulation (use 6th edition Figure 43.7, unchanged)

Antibodies against MuSK mimic myasthenia gravis

Antibodies cause calcium channel dysfunction in Lambert-Eaton syndrome

Potassium channel antibodies in Isaacs syndrome cause neuromyotonia

TOXINS AND METABOLITES THAT ALTER MUSCULAR EXCITATION

Bacterial botulinum toxin blocks presynaptic ACh release

Dinoflagellates synthesize tetrodotoxin and saxitoxin to block the sodium channel

Scorpion, snail, spider and snake peptide venoms act on multiple molecular targets at the neuromuscular junction

Electrolyte imbalances alter the voltage sensitivity of muscle ion channels

REFERENCES

45. Disorders of Basal Ganglia

Mahlon DeLong ***medmrd@emory.edu***

Thomas Wichman ***twichma@emory.edu***

1. Anatomy and normal function of the basal ganglia

2. Parkinson's disease

3. Huntington's disease

4. Wilson's disease

4. Dystonia

5. Drug- and toxin-induced movement disorders

We will also emphasize neuroprotective and restorative strategies as appropriate in these subsections (particularly, of course, with regard to Parkinson's and Huntington's disease).

46. NEURODEGENERATIVE α-SYNUCLEINOPATHIES AND TAUOPATHIES.

Michel Goedert and *Maria Grazia Spillantini*
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49. Molecular Biology of Vision

Hitoshi Shichi Hshichi@msn.com

50. Molecular Biology of Olfaction and Taste

Steven D. Munger **smunger@som.umaryland.edu**

OLFACTION

The mammalian olfactory system possesses enormous discriminatory power.

The initial events in olfaction occur in a specialized olfactory neurepithelium.

Odor discrimination could involve a very large number of different odorant receptors, each highly specific for one or a small set of odorants.

The information generated by hundreds of different receptor types must be organized to achieve a high level of olfactory discrimination.

The sensitivity of the olfactory system is likely to derive from the capacity of the olfactory transduction apparatus to effectively amplify and rapidly terminate signals.

Odorant recognition initiates a second-messenger system leading to the depolarization of the neuron and the generation of action potentials.

Negative feedback mechanisms mediate adaptation of the olfactory transduction apparatus to prolonged or repetitive stimulation.

Alternative second-messenger pathways may be at work in olfactory transduction.

The vomeronasal organ is an accessory chemosensing system that plays a major role in the detection of conspecific chemical cues, also known as pheromones.

Chemosensory neurons of the vomeronasal system are narrowly tuned to specific chemical cues, and utilize a unique mechanism of sensory transduction.

TASTE

Multiple senses, including taste, contribute to our total perception of food.

Taste receptor cells are organized into taste buds.

Sensory afferents within three cranial nerves innervate the taste buds.

Information coding of taste is not strictly according to a labeled line.

Taste cells have multiple types of ion channels.

Salts and acids are transduced by direct interaction with ion channels.

Taste cells contain receptors, G proteins and second-messenger-effector enzymes.

Sweet, bitter and umami involve receptor-coupled second-messenger pathways that are differentially expressed across the gustatory epithelium.

Gustducin is a taste cell-specific G protein closely related to the transducins.

51. Mechanotransduction

Peter G. Gillespie gillespp@ohsu.edu

WHAT IS MECHANOTRANSDUCTION?

Utility of mechanotransduction for organisms

Types of mechanotransduction

Unified model for mechanotransduction

MODEL SYSTEMS

Advantages to use of model systems

C. elegans touch receptors

C. elegans polymodal sensory neurons

Drosophila bristle receptors and chordotonal organs

Evolutionary relationships with vertebrate mechanoreceptors

HAIR CELLS

Auditory and vestibular systems: role of hair cells

Basic hair-cell transduction mechanism

Molecular characterization of hair-cell transduction

DEAFNESS

"Deafness gene" approach

Identified genes (focus on Usher genes)

Relationship to transduction (no transduction genes identified yet?)

OTHER VERTEBRATE MECHANORECEPTORS

Cutaneous mechanoreceptors

Baroreceptors

Others

SUMMARY AND FUTURE DIRECTION

52. Endocrine Effects in the Brain and Their Relationship to Behavior

Bruce S. McEwen

53. MOLECULAR BASIS OF LEARNING AND MEMORY

Joe Z. Tsien **jtsien@princeton.edu**

Brief History of Memory Research: The Penfield Studies

Amnesia in H.M. and Temporal Lobe

Declarative Memory vs. Procedural Memory

Short-Term Memory vs. Long-Term Memory

Hebb's Rule and the NMDA receptor

Long-Term Potentiation

Long-Term Depression

Molecular Switch of Learning

Molecular Basis of Long-Term Memory

Systems Level of Memory Consolidation and Storage

Learning and Memory Enhancement

54. Neurobiology of Schizophrenia

Joseph Coyle
joseph_coyle@hms.harvard.edu

I. Clinical aspects of schizophrenia

A. Schizophrenia, bipolar disorder and psychotic depression are the major forms of psychotic disorders

B. Psychopathology of schizophrenia comprises positive symptoms, negative symptoms and cognitive impairments

C. Dominant treatment for 50 years are the D2 blocking antipsychotic drugs
1. typical antipsychotics
2. atypical antipsychotics
3. clozapine

II. Etiology

A. Epidemiology

B. Genetics – a disorder of multiple genes of small effect

C. Role of development
1. neuronal migratory defects
2. perinatal insults

D. Brain abnormalities in
1, reduced cortical volume
2 abnormal activation with specific tasks

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III. Pathophysiology

A. Dopamine
1. mechanism of action of antipsychotics
2. functional abnormalities in dopamine
   a. cortical
   b. subcortical

B. GABAergic
1. evidence of hypofunction
2. down regulation of presynaptic markers
3. possible loss or migratory deficits

C. Glutamate
1. dissociative anaesthetics and the endophenotype
2. genetic and post-mortem findings of NMDA receptor hypofunction
3. impact of glycine modulatory site agonists on symptoms

D. Acetylcholine
1. linkage to an allelic variant of alpha 7 nicotinic receptor
2. alpha 7 nicotinic receptor and cognitive functions

IV. Conclusion

References

55. NEUROBIOLOGY OF SEVERE MOOD AND ANXIETY DISORDERS

John J Mann & Husseini K Manji

MOOD DISORDERS

- INTRODUCTION
- MORBIDITY AND MORTALITY
- DEPRESSION AND BIPOLAR DISORDER ARISE FROM INTERACTIONS BETWEEN SUSSCEPTIBILITY GENES AND ENVIRONMENTAL FACTORS
- MULTIPLE NEUROTRANSMITTER AND NEUROPEPTIDE SYSTEMS ARE IMPLICATED IN THE PATHOPHYSIOLOGY AND TREATMENT OF MOOD DISORDERS
    - Serotonergic System
    - Noradrenergic System
    - Dopaminergic System
    - Cholinergic System
    - Glutamatergic System
    - GABAergic System
    - CRH/HPA Axis
    - Other Neuropeptides
- ABNORMALITIES OF CIRCADIAN AND OTHER RHYTHMS
- NEUROANAMTOMICAL AND NEUROPATHOLOGIC CORRELATES OF MOOD DISORDERS
- STRESS & GLUCOCORTICOIDS MODULATE NEURAL PLASTICITY: IMPLICATIONS FOR SEVERE MOOD DISORDERS
- SIGNALING PATHWAYS ARE INVOLVED IN THE PATHOPHSYIOLOGY AND TREATMENT OF SEVERE MOOD DISORDERS
    - ❖ cAMP Generating System

next page

- ❖ Phosphoinositide/PKC Signaling Cascade
- ❖ Wnt Signaling Cascade
- ❖ Neurotrophic Signaling Cascades

ANXIETY DISORDERS

- INTRODUCTION AND CLASSIFICATION

- ANIMAL MODELS OF FEAR/ANXIETY
  Issues of Validity of Models

- GENETIC STUDIES OF ANXIETY IN MICE

- NEUROCHEMISTRY OF FEAR AND ANXIETY

  - ❖ Noradrenergic System
  - ❖ Serotonergic System
  - ❖ GABAergic System
  - ❖ Neurosteroids
  - ❖ CRF and the Stress Axis
  - ❖ NPY & other Neuropeptides
  - ❖ Intracellular Cascades

- CONCLUDING REMARKS: FUTURE DIRECTIONS & THE DEVELOPMENT OF NOVEL THERAPEUTICS

- REFERENCES

- ADDITIONAL REFERENCES

56. ADDICTION

Marina Wolf

I. Basic definitions

A. Addiction: compulsive drug craving and administration despite tremendous adverse consequences
B. Tolerance: The need for an increasing dose of drug to achieve the same effect
C. Sensitization: Enhancement of some drug responses as a result of repeated drug exposure
D. Dependence: Physical dependence refers to an altered physiological state resulting from repeated drug exposure, such that cessation of drug use leads to a somatic withdrawal syndrome. Psychological dependence refers to emotional or motivational symptoms that follow drug withdrawal. Depending on the drug in question, both physical and psychological dependence can contribute importantly to compulsive drug craving.

II. Natural reinforcers and drugs of abuse use similar circuitry

A. Early theories of behavior emphasized importance of reducing aversive states, e.g., reinforcers such as eating or drinking can shape behavior because they reduce aversive states (hunger and thirst). Current theories emphasize the ability of rewards to act as incentives, causing neural representations that elicit motivation and pursuit of goals.
B. Drugs of abuse "usurp" neural circuits that mediate incentive value of natural reinforcers, so studying neurobiology of natural reinforcers is important for understanding addiction.
C. The major substrate for natural reward is the mesocorticolimbic dopamine (DA) system (*Fig. 1: reward circuits*). Most research focuses on DA neurons in ventral tegmental area (VTA) that project to the nucleus accumbens (ventral striatum). Nucleus accumbens neurons receive inputs from limbic and cortical regions that convey motivational information; they project to motor regions. Hence, nucleus accumbens has been described as an interface between limbic and motor systems, where motivation is converted to action. However, DA neurons in the substantia nigra, which project primarily to dorsal striatum, also participate in reward circuitry. Recent work has focused on their role in the performance of habitual behaviors associated with addiction.
D. Natural rewards activate these midbrain DA neurons. So do all drugs of abuse, but different drugs have different targets in brain and thus use different mechanisms to activate DA neurons. Psychostimulants directly increase DA transmission by blocking DA uptake and/or promoting release, while opiates, nicotine and ethanol do so indirectly by interacting with other transmitter systems that regulate DA cell activity. Three important transmitters for regulation of DA cell activity at the level of the VTA are glutamate, GABA and acetylcholine [*Fig. 2 will show important inputs/mechanisms regulating VTA DA cell activity, and illustrate how various addictive drugs tap into these mechanisms]*.
E. What is the actual role of DA in mediating reinforcement? Originally, DA was suggested to mediate the pleasure evoked by rewarding stimuli, but it was shown in 1980's that animals lacking DA, due to lesions, still emitted responses indicating that they "liked" or "didn't like" particular tastes. Accordingly, two major current theories:

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1. DA neurons "learn and predict" the occurrence of rewards, and thus participate in the ongoing learning of adaptive behaviors (Schultz, DiChiara). Fits well with ability of DA (and drugs of abuse) to promote stimulus/reward learning on a behavioral level and modulate neuronal plasticity on a cellular level.
2. DA neurons attribute incentive salience to rewards and to conditioned stimuli associated with rewards, enhancing the extent to which they are "wanted" and can therefore shape behavior (Robinson and Berridge). This theory has spawned the useful adage that DA mediates "wanting" not "liking". Repeated administration of drugs of abuse is proposed to sensitize the DA-dependent systems that mediate incentive salience, leading to pathological intensification of drug "wanting".
3. Both theories help explain how chronic drug exposure facilitates the formation of new habits that center around drug-seeking behavior, usually at the expense of more appropriate behaviors. They also help explain the powerful ability of drug-related cues to drive drug-seeking behavior and promote relapse even after long periods of abstinence.

F. While these theories are important, addiction cannot be conceptualized simply as an enhancement of DA-regulated incentive-motivational processes.
   1. The desire to overcome aversive effects associated with withdrawal may also contribute to compulsive drug-seeking in addicts, particularly in the short run.
   2. Addiction is characterized by cognitive dysfunction (impulsivity, loss of behavioral inhibition) as well as motivational dysfunction.
   3. Altered stress responses contribute to addiction. Repeated drug exposure increases vulnerability to stress, and stress is a powerful trigger for drug-taking in addicts and relapse in recovering addicts. A common element of withdrawal syndromes produced by several drugs of abuse is elevation of CRF levels in the mesolimbic system, which may mediate stress-like symptoms of withdrawal.
   4. Individuals differ greatly in their vulnerability to drugs of abuse – this is a topic of intense research.

G. The role of DA neurons in reward/addiction has to be studied within the context of the complex neuronal circuits within which the DA neurons are embedded. Many reciprocal connections exist between limbic, cortical and motor regions (*see Fig. 1*). Important points to make:
   1. A general rule is that neurons receiving DA inputs (e.g., nucleus accumbens neurons) also receive convergent glutamate and GABA inputs. These inputs are the primary determinants of neuronal excitability. DA plays a modulatory role, albeit a critical one, by influencing synaptic transmission and modulating voltage-dependent conductances.
   2. After chronic drug administration, many important adaptations occur downstream of DA neurons, and involve multiple transmitter and signal transduction systems.

II. Classes of Addictive Drugs

A. Stimulants (cocaine and the amphetamines)
   1. Cocaine, amphetamine, methamphetamine, MDMA, methylphenidate: Behavioral effects, addictive potential, withdrawal syndrome

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2. Initial targets in brain: monoamine transporters (DAT, SERT, NET). Different stimulants interact differently with transporters. Cocaine is a monoamine uptake inhibitor. Amphetamine and its derivatives are competitive inhibitors of monoamine uptake but also substrates for monoamine transporters; through the latter mechanism they promote DA efflux by reverse transport. They also promote redistribution of DA from synaptic vesicles to the cytosol by collapsing vesicular pH gradient (weak base mechanism). Very recent studies suggest that amphetamine can also cause DAT internalization, a novel mechanism for regulating DA uptake. Different stimulants differ somewhat in relative affinities for DAT, SERT and NET. Amphetamine – almost equal affinities for DAT and NET, lower for SERT. Cocaine: higher for SERT and DAT then NET. Interaction with DAT is most critical for rewarding effects of cocaine but SERT also plays a role. Methamphetamine: DAT > SERT. MDMA: DAT and SERT about equal. Methylphenidate (Ritalin) – highest at DAT.
3. New ideas in stimulant research:
    i. MDMA and METH lead to permanent impairments of memory/impulsivity that are linked to their neurotoxic effects on serotonin systems.
    ii. Methylphenidate (Ritalin) exposure may enhance reactivity and vulnerability to other drugs of abuse, e.g. cocaine, later in life. The implications of this are quite serious as Ritalin is widely prescribed for treatment of attention deficit hyperactivity disorder (ADHD), the most commonly diagnosed disorder of childhood.
4. Mechanisms of stimulant action: Blockade of monoamine transporters enhances monoamine transmission – increased DA transmission most closely linked to rewarding effects. I will briefly review DA receptor subtypes unless this is covered elsewhere in the book (??). D1 and D2 receptors play key roles. D1 receptors are positively coupled to adenylyl cyclase, D2 receptors are negatively coupled. Through the cAMP-PKA pathway, DA receptor signaling influences cellular targets that regulate neuronal excitability (e.g., ligand and voltage-gated ion channels) as well as targets that contribute to long-term adaptations (transcription factors such as CREB). [*I will expand on this section with the help of a diagram – Fig. 3 - that will include DARPP32, cdk5, etc, and also illustrate possible interactions with glutamatergic signaling – based on similar diagrams in Greengard's reviews*].
5. Long-term adaptations involve a cascade of changes involving different transmitter systems and different brain regions at different withdrawal times. Shortly after discontinuing stimulant administration, DA neurons are hyperexcitable due to several mechanisms, possibly including LTP at glutamate synapses onto DA neurons. This is transient, but serves to trigger longer-lasting changes in downstream pathways. For example, changes in glutamate transmission occur throughout the mesocorticolimbic system. AMPA transmission in the nucleus accumbens seems particularly important in driving cocaine-seeking behavior in rats. On a cellular level, upregulation of the D1-cAMP-PKA-CREB pathway in nucleus accumbens may play a role in some adaptations. Prolonged D1 receptor activation increases expression of dynorphin,

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an endogenous opioid peptide encoded by a CREB-regulated gene. Dynorphin binds to _ opioid receptors on DA nerve terminals, producing a decrease in DA release that may contribute to dysphoria during withdrawal.

B. Opiates

1. Opium, extracted from poppy plants, has been used for recreational and medicinal purposes for thousands of years. Morphine identified as active pharmacological ingredient in early 1800's. Heroin synthesized from morphine in late 1800s in attempt to develop non-addicting cough suppressant. Heroin is more lipophilic than morphine, therefore produces effects more rapidly. The term "opioid" is more inclusive, encompassing natural derivatives of opium such as morphine, synthetic morphine-like drugs including heroin, and the endogenous opioid peptides (endorphins, endomorphins, enkephalins, dynorphins).
2. Acute behavioral actions: analgesia, autonomic inhibition and "high". All effects show tolerance. Severe withdrawal syndrome, with physical and psychological components. The mesocorticolimbic system is important for acute rewarding effects and psychological withdrawal symptoms/craving. Opiate actions in spinal cord and brain stem are responsible for analgesic and autonomic effects of opiates and bulk of physical withdrawal symptoms – a particularly important area for physical withdrawal syndrome is the locus coeruleus (LC), the major noradrenergic nucleus in brain. Located in the brainstem, the locus coeruleus regulates autonomic function and attentional states.
3. Initial targets in brain: three opioid receptor types (_,_,_). The _-opioid receptor is critical for rewarding effects of opioids. Generally mediates neuronal inhibition (briefly review signal transduction pathways). Effects in VTA and nucleus accumbens are particularly important. In VTA, opioids activate DA neurons through an indirect mechanism – they stimulate _-opioid receptors on VTA GABA neurons that synapse on VTA DA neurons. This inhibits the GABA neurons, leading to disinhibition of the DA neurons and DA release in NAc and other target areas (Fig. 1). Opiates also directly affect NAc neurons independently of dopamine by activating opioid receptors on the NAc neurons themselves. Relative contribution of these two sites of action to rewarding effects of opiates is still not clear. There is increasing evidence that endogenous cannabinoid systems are also important in mediating the rewarding effects of opiates and vice versa.
4. Neurobiology of physical withdrawal syndrome: During chronic opiate administration, LC neurons develop tolerance to acute inhibitory effects of opiates, so upon removal of opiates (withdrawal) they exhibit a dramatic rebound increase in activity. This increase in NE transmission is responsible for many withdrawal symptoms. A cellular mechanism that contributes importantly to rebound activation of LC neurons has been worked out (one of first addiction-related mechanisms to be understood at cellular/signal transduction level; Nestler). Opiates inhibit LC neurons in part through inhibition of adenylyl cyclase (which leads to inhibition of a nonspecific cation current). During chronic opiate administration, expression of adenylyl cyclase and PKA in the LC is increased, which increases the excitability of the neurons, enabling them to return to normal

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firing rates despite continued presence of opiates. When drug is withdrawn, up-regulation of the cAMP pathway is no longer opposed by inhibitory effects of opiates, leading to abnormally high firing rates of LC neurons.

5. Craving and psychological dependence: In nucleus accumbens, chronic opiate treatment leads to downregulation of _-opioid receptors and upregulation of cyclic AMP-PKA pathway, increasing CREB-mediated dynorphin transcription. Dynorphin stimulates presynaptic _ receptors on DA nerve terminals, inhibiting DA release and contributing to dysphoria. Note that upregulation of cAMP-PKA-CREB signaling also implicated in adaptive responses to chronic stimulant administration (above). In addition, adaptations in CRF neurons may contribute to anxiety of withdrawal and vulnerability to stress-induced relapse.
6. Two main treatments for opiate withdrawal syndrome: 1) replacement therapy with methadone or other _ agonists – longer half-life than heroin or morphine, produce mild stimulation rather than euphoria. Also produces cross-tolerance to heroin, lessening its effect if patients relapse. 2) _2 agonist clonodine (many autonomic effects of opiate withdrawal are due to loss of opioid inhibition of NE neurons).

C. Phencyclidine (PCP, angel dust)
    1. A dissociative anesthetic, similar to ketamine. Produces powerful euphoric effects as well as dysphoric effects in humans. PCP and ketamine mimic both positive and negative signs of schizophrenia in humans.
    2. Mechanism of action: long known to be a weak DA uptake blocker, but more recently it has been established that its major mechanism of action involves noncompetitive antagonism of NMDA-type glutamate receptors. This realization, coupled with its ability to mimic schizophrenic symptoms, was an important impetus for glutamate-based theories of the pathogenesis of schizophrenia (is this covered elsewhere in the book? – if so, I won't say too much about PCP in the addiction chapter). PCP can activate DA neurons indirectly, through blockade of NMDA receptors that influence DA neuron activity, but many of its actions related to rewarding effects appear to be dopamine-independent. Also produces neurotoxicity through NMDA receptor blockade.

D. Marijuana (cannabinoids)
    1. Derivatives of *Cannabis Sativa L.*, such as marijuana and hashish, have been used for centuries for recreational and therapeutic purposes. Rapid progress in recent years due to:
        i. Cloning of G-protein coupled receptors for cannabinoids (CB1 in brain, CB2 in periphery), development of increasingly specific antagonists for these receptors, and development of CB1 and CB2 knockout mice
        ii. Identification of endogenous cannabinoids (endocannabinoids), synthetic and hydrolyzing enzymes for cannabinoids, and transporters for cannabinoids – these have been used to define cannabinoid-utilizing brain pathways.
    2. The psychoactive component of cannabis is Δ^9tetrahydrocannabinol (THC). THC, as well as cannabimimetics and endocannabinoids, mediate their actions in

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the central nervous system through CB1, a Gi/Go-protein coupled receptor that is widely distributed in brain and has been shown to inhibit adenylate cyclase, activate MAP-kinases, reduce Ca^{++} currents, and modulate several K^{+} conductances. Activation of CB1 receptors inhibits synaptic transmission in many brain regions.

3. Behavioral effects: Acute effects in humans include euphoria, giddiness, relaxation, sedation and sometimes anxiety, paranoia and panic. Abrupt cessation of heavy marijuana use can produce a cannabinoid withdrawal syndrome characterized by drug craving restlessness, irritability, agitation, insomnia, nausea and cramping. Initially, behavioral studies of cannabinoids in animals were complicated by difficulty in demonstrating rewarding effects in common animal models, due to prominent aversive effects at higher doses. However, direct reinforcing properties are now established, as well as tolerance and dependence.
4. Neurobiological basis of reinforcing effects of cannabinoids: Mediated by CB1 receptors but involve actions on multiple systems. Regulation of mesolimbic DA system is important. In VTA, cannabinoids activate presynaptic CB1 receptors that inhibit GABA release, which disinhibits the DA neurons. In the nucleus accumbens, cannabinoids also activate presynaptic CB1 receptors that depress glutamate and GABA release. There may also be postsynaptic interactions between DA receptors and CB1 receptors. In addition to DA systems, endogenous opioid systems play an important role in reinforcing effects of cannabinoids, as opioid antagonists block cannabinoid self-administration in monkeys and rodents. This interaction between cannabinoids and opioid systems is bi-directional (see section on opioids) and is important not only for rewarding effects but also for withdrawal syndromes.
5. Neurobiological basis of withdrawal syndrome: Similar to opioids, cannabinoid withdrawal is associated with upregulation of cAMP pathway. But this occurs mainly in the cerebellum (an important region for movement coordination), which may account for milder somatic symptoms associated with cannabinoid as compared to opioid withdrawal. Motivational and emotional effects of cannabinoid withdrawal may be related to alterations in CRF function in limbic system (stress-like symptoms) and reduction in DA transmission (dysphoric and aversive effects).
6. Long-term adaptations: Very recent work suggests a role for endocannabinoids in synaptic plasticity in the reward circuitry. They are necessary for induction of LTD in the striatum and nucleus accumbens (Lovinger, Manzoni).

E. Ethanol and anxiolytics/sedatives
    1. Alcoholism is a complex disorder influenced by genetic, environmental and neurobiological factors. Withdrawal from chronic alcohol intake is accompanied by severe somatic symptoms. Alcoholism is characterized by chronic vulnerability to relapse after long after cessation of drinking.
    2. Ethanol has many physiological effects in brain, including influences on membranes, ion channels and multiple neurotransmitter receptors. Recent work has focused on the ability of ethanol to act as a positive allosteric modulator of $GABA_A$ receptors and a negative allosteric modulator of NMDA receptors.

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However, as $GABA_A$ and NMDA receptors are highly expressed throughout reward circuitry, this doesn't help to identify potential sites of ethanol action within this circuitry. This has complicated studies of the neurobiology of ethanol addiction.

3. Role of DA systems in ethanol action: Activation of DA neurons is an important contributor to the reinforcing effects of ethanol. By enhancing $GABA_A$ receptor transmission in VTA, VTA GABA neurons are inhibited, which disinhibits the DA neurons. Ethanol may also directly excite DA neurons. After chronic ethanol exposure, adaptations apparently develop in mesolimbic DA function to offset excitatory effects of ethanol, such that withdrawal from chronic ethanol leads to decreases in DA cell activity and extracellular DA levels in nucleus accumbens. Drinking during withdrawal may be "motivated" by need to reverse DA deficits.
4. Role of other transmitter systems: Opioid systems also play an important role in the addictive actions of ethanol, as antagonists of _ and _ opioid receptors decrease ethanol consumption and reinforcement. Some effects of opioid systems may involve interactions with DA transmission in the nucleus accumbens. On the basis of animal studies, the opiate antagonist naltrexone has been used as a treatment for alcoholism. Recent work suggests that cannabinoid systems and neuropeptide Y may also be involved in ethanol reinforcement and consumption. Adaptations in CRF systems in the extended amygdala may contribute to anxiety and other affective changes in withdrawal.
5. Sedatives such as the barbiturates were used for the treatment of anxiety in the early in the 20^{th} century. Benzodiazepines were introduced in the early 1960's. Both drug classes have abuse liability, although less than stimulants and opiates. There is cross-tolerance and cross-dependence among ethanol, barbiturates and benzodiazepines, as all are positive allosteric modulators of $GABA_A$ receptors, and produce down-regulation of $GABA_A$ receptors after chronic treatment. Accordingly, benzodiazepines are commonly used, both in the clinic and on the street, to treat symptoms of alcohol withdrawal.

F. Nicotine
    1. Nicotine is responsible for reinforcing effect of tobacco products. Highly addictive - addiction results in 30% of those who experiment with tobacco products. One year after quitting, abstinence rate only 20%. Nicotine withdrawal syndrome is characterized by nicotine craving as well as dysphoria, anxiety, irritability, restlessness and increased appetite. Treated with nicotine replacement therapies, such as nicotine gum and patches, and/or with buproprion, a drug that is classified as an antidepressant but has multiple and complex effects in brain. Buproprion reduces craving in some smokers.
    2. Targets in brain: Nicotine is an agonist at the nicotinic acetylcholine receptor, an ionotropic receptor that passes sodium and calcium, leading to depolarization of target cells. Nicotine receptors are pentamers, composed of different combinations formed by 12 neuronal subunit gene products (_2- _10 and _2- _4). Of these, a subset is expressed in the VTA (_3-7 and _2-4). It is thought that _7 receptors form homomeric receptors; _3, _4 and _6 form heteromeric channels with _2 or _4; and _5 and _3 can associate with other _/_ pairs. Most VTA DA

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neurons possess two types of _2 containing receptors, and include _4 as well as other subunits. About 40% of VTA DA neurons also express an _7 containing receptor.

3. Rewarding and addictive effects linked to activation of DA neurons in the ventral tegmental area: Studies in knockout mice implicate several subunits in the ability of nicotine to modulate DA neurons (_4, _6, _7, _2, _3) but suggest that _2 containing receptors play a critical role, as they necessary for nicotine-induced increases in DA release in VTA target areas and for nicotine self-administration. _2 containing receptors are present on DA and GABA cells in VTA, while _7 containing receptors are present on glutamate nerve terminals in VTA. A critical question is how nicotine produces rewarding effects given that high affinity nicotinic receptors, including the _2-containing receptors on DA and GABA cells of the VTA, are rapidly desensitized by blood nicotine levels attained during smoking. Initially nicotine excites DA neurons directly via activation of nicotinic receptors on DA cells and indirectly via activation of presynaptic _7 containing receptors that promote glutamate release. Excitation of GABA cells likely offsets this initial excitation to some degree. But within minutes, the _2 receptors on the DA cells and GABA cells desensitize. However, the _7 receptors desensitize to a lesser extent and continue to promote glutamate release, which now excites the DA cells even more effectively given the decrease in inhibitory GABA synaptic inputs. By enhancing glutamate release, presynaptic _7 receptors in VTA also promote LTP, providing a mechanism whereby nicotine may initiate synaptic plasticity in the VTA. This may contribute to long-term adaptations in the reward circuitry that underlie nicotine addiction. Consistent with demonstration that both NMDA and nicotinic acetylcholine receptor activation are required for development of nicotine-induced behavioral sensitization. Interestingly, both are also required for development of cocaine- and amphetamine-induced behavioral sensitization and nicotinic receptors are also implicated in cocaine's ability to produce conditioned place preference, another model for addiction. Makes sense in that acetylcholine projections (originating from mesopontine nuclei, PPT and LDT) are important regulators of VTA DA cell activity, thus cholinergic transmission likely to contribute to effects of other drugs of abuse.

III. Addiction and neuronal plasticity utilize common cellular mechanisms

A. An important current hypothesis is that adaptations leading to addiction involve the same glutamate-dependent cellular mechanisms that operate during learning and memory. In other words, addiction can be viewed as a form of neuronal plasticity – a very persistent form, as a high risk of relapse persists even after years of abstinence. This view of addiction is supported by several lines of evidence.
    1. Effects of chronic drug administration involve different circuits than acute drug reward – human and animal imaging studies suggest that brain regions implicated in learning and memory are activated during drug craving. Consistent with important role of conditioned responses and learned associations in drug craving.
    2. Glutamate, the key transmitter for neuronal plasticity, has been shown to play a key role in animal models of addiction (e.g., behavioral sensitization). Many

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drug-induced adaptations require glutamate transmission for their development, whereas their expression is associated with altered glutamate transmission.

3. LTP and LTD may contribute to reorganization of neuronal circuits in both addiction and learning. For example, many drugs of abuse (and stress) have in common the ability to produce LTP in VTA DA neurons, producing a transient activation of DA neurons that is believed to trigger downstream adaptations that are more persistent. Drugs of abuse may influence LTP and LTD through PKA-dependent cascades that regulate glutamate receptor trafficking.
4. Studies at the cellular and molecular levels have demonstrated that common mechanisms are engaged during repeated drug administration and during learning, including common signal transduction cascades (e.g., protein kinase and phosphatase cascades, CREB, neurotrophic factors) and synaptic remodeling (changes in dendritic branching, spine density and number of branched spines).

B. Candidates for mediating persistent reorganization of neural transmission in addiction
    1. Changes in gene expression, leading to altered activity of neurons expressing these genes and ultimately to alterations in the activity of neuronal circuits. Two transcription factors are strongly implicated in addiction – CREB and ΔFosB. These factors mediate both homeostatic and sensitizing adaptations following repeated drug exposure. However, their levels return to normal after relatively short withdrawal periods (weeks-months). Thus, most likely that they are triggers for stable changes that occur through other mechanisms.
    2. Synaptic remodeling. Drugs of abuse (cocaine, amphetamine, morphine, nicotine) alter dendritic branching, spine density and spine branching in nucleus accumbens and prefrontal cortex. These effects are among the most long-lasting reported in response to chronic drug administration and are therefore good candidates for mediating its persistence. According to some theories, LTP is the first step in a cascade leading to structural changes in synapses. Thus drugs of abuse, by regulating LTP, may ultimately lead to synaptic remodeling. Drug-induced increases in neurotrophic factor expression may also contribute to alterations in dendritic morphology.
C. Challenge is to relate plasticity on cellular and molecular level to behavioral alterations that drive addiction (circuit level). For example, how do drug-associated cues acquire heightened ability to control behavior in drug addicts? Why are inhibitory control mechanisms impaired in addicts? If we identify pathways that are re-wired and know something about the pharmacology of systems that regulate specific pathways, perhaps pharmacological treatments can be devised to reduce craving and relapse.

57. PAIN

Woolf, Costigan, Samad and Scholz

Define nociceptive, inflammatory functional and neuropathic pain and clinical physiological significance. Mention cancer pain as a composite of these syndromes

Identify mechanisms responsible for pain:

Transduction – nociceptor terminal
- Transduction receptor/ion channels TRPs/ASICs/P2x
- Peripheral sensitization Cox/Bradykinin/NGF PKA and PKC mediated phosphorylation/increased trafficking of receptor to terminal

Conduction primary sensory neuron/projection pathways
- Sensory neuron VGScs TTXs TTXR – local anesthetic action
- Ectopic excitability – VGSC, K channel – anticonvulsants/adrenergic receptor expression and sensitivity sympathetic drive

Transmission dorsal horn/brain stem/thalamus/cortex
- Excitation fast/slow glutamate/ATP/peptides
- Inhibition pre postsynaptic GABA/glycine/NA/Opioids local/descending

- Central sensitization early/late sickness syndrome
- Disinhibition

Perception
- Perceptual/cognitive/emotional/social/cultural element placebo/fMRI

Emphasize temporal features
- excitation *ms*
- use dependent plasticity postranslational modification/trafficking/internalization *seconds*
- transcriptional translational control phenotypic switches *days*
- structural sprouting cell death *months/years*

Genetic determinants
- Gender
- channelopathies

58. Magnetic Resonance Spectroscopy and Positron Emission Tomography

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INTRODUCTION

Brief history of MRS
Overview/scope of chapter

METHODS in MRS

1D-methods: pulse-acquire, spin-echo, J-editing, quantum-filters, decoupling
2D-methods: J-resolved echo

Single-voxel localization: PRESS, DRESS, STEAM, ISIS, LASER
Multi-voxel localization: CSI, HADAMARD, EPI

Time-domain fitting vs Frequency-domain Quantitation

BIOCHEMICAL AND PHYSIOLOGICAL MEASUREMENTS USING MRS

Proton (1H): membranes/neurodegeneration (NAA, choline)
glucose-metabolism (glutamine/glutamate)
energy-metabolism(pyrimidines, lactate)
neurotransmitter function (GABA, glx)

Phosphorus (31P): membrane-metabolism (phosphomonoesters, phosphodiesters)
energy-metabolism (inorganic phosphate, phosphocreatine, NTP)

Carbon-13 (13C): glucose-metabolism (glutamine, glutamate)

Sodium (23Na): intercellular vs extracellular Na concentrations

Lithium (3Li): 3Li-containing drug uptake

Flourine (19F): 19F-containing drug uptake

CLINICAL APPLICATIONS OF MRS

Studies of neuropsychiatric disorders: schizophrenia, depression, bipolar-disorders, Tourrette's Syndrome, autism, anxiety/panic disorders, dyslexia, substance-abuse/alcoholism, sleep disorders

Studies of neuropathological disorders: epilepsy, Alzheimer's, Parkinson's, multiple-sclerosis, stroke, cancer, mitochondrial dysfunction, brain-injury

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Positron Emission Tomography

I. INTRODUCTION

A. In Vivo vs. In Vitro measures

1. Basic functions measured (metabolism, blood flow, blood volume, receptors, neurotransmitters)

II. METHODS

A. Radiotracers used for brain function

1. Single photon vs. positrons

2. Generator vs. cyclotron produced radioisotopes (including the maximum energy. range of particles, half-life or single/annihilation photons

III.DETECTION OF RADIOACTIVITY FOR BRAIN IMAGING

A. PET compared to SPECT

1. Crystals, reconstruction, correction for attenuation, scatter, randoms, etc.

B. ADVANTAGES AND DISADVANTAGES OF PET VS SPECT

C. RESOLUTION AND SENSATIVITIY OF PET/SPECT

1. Table and description of typical resolution sensitivity for PET/SPECT autoradiography, MRI, PET/SPECT

IV. FUNDAMENTALS OF RADIOTRACER METHODOLOGY

A. Basic radiochemistry for PET, SPECT- principals of labeling with radioisotopes and typical successful "ligands"

V. Validation of radiotracers

A. In Vitro vs. In Vivo rodent study

1. Typical validation for radiochemical and radiopharmaceutical purity.

VI. Role of Mathematical Modeling for Quantification

A. Differences Between Simple Tissue Time Activity Curve and Model Parameters with Examples, e.g., FDG, Glucose Metabolism, Blood Flow and Receptors Measures Of Binding Potential and Receptor Density

B. Limitation – Partial Volume Effect; Non-Specific Binding; Anatomical Vs. Functional Resolution; Ionizing Vs. Non-Ionizing Radiation and Risk to Subjects

VII. APPLICATIONS FOR BRAIN FUNCTION

A. THE SIMPLIST BRAIN FUNCTION (BLOOD VOLUME CEREBRAL BLOOD FLOW)

B. GLUCOSE AND OXYGEN MATABOLISM

1. The hexokinase step and principals of measuring the rate-limiting step as part of modeling.

C. NEURORECEPTOR IMAGING

1. Principals based *in vivo and in vitro* receptor binding and pharmacologic validation.

a) Quantification of receptors including saturation pharmacological competition studies

b)

VIII. CLINICAL APPLICATIONS

A. CNS DRUG DESIGN AND PRECLINICAL/CLINICAL DRUG DEVELOPMENT

1. **Investigation of receptor distribution / site of action**
2. **Effects of drugs on metabolism, blood flow and receptor binding**
3. **Estimating drug doses based on receptor occupancy**

IX. CLINICAL APPLICATIONS

A. CEREBRAL BLOOD FLOW VS. STROKE

1. **FDG and SPECT / Epilepsy**
2. **FDG/Cerebral Blood Flow and Cognitive Evaluation Studies**

X. NEUROPSYCHIATRIC APPLICATIONS

A. Neuroreceptor and FDG

B. Aging; Psychoses; Depression; Parkinson; Alzheimer's; Mental Retardation;

XI. SMALL ANIMAL PET/SPECT

A. Receptor Binding Role of knockout mice and future directions

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REFERENCES