Basics of Behavioral Neurochemistry

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SLIDES

http://cmrr.umn.edu/~kelvin/ismrm2002
Neurochemistry

? 

Behavior
GOAL

Provide a framework for thinking about behavior and neurochemistry
BEHAVIOR

Broad definition
• motor
• cognition
• affect
• disease

How does neurochemistry relate to these behaviors?
OBJECTIVES

- Name 5 neurotransmitter systems and a behavior associated with each one
- Identify drugs which act on each of the 5 neurotransmitter systems
- Be aware of how MR is being used in the study of neurotransmitters
- Finish in time for lunch!
PRETEST:
Match the NT to the behavior

1. Dopamine       A. Alzheimer’s disease
2. Serotonin      B. epilepsy
3. Acetylcholine  C. depression
4. GABA           D. Schizophrenia
5. Glutamate      E. Parkinson’s disease
PRETEST:
Match the NT to a drug

1. Dopamine  
   A. diazepam (Valium)
2. Serotonin  
   B. donepezil (Aricept)
3. Acetylcholine  
   C. Phencyclidine
4. GABA  
   D. fluoxetine (Prozac)
5. Glutamate  
   E. Cocaine
PRETEST:
Match the NT to the MR method

1. Dopamine  A. BOLD
2. Serotonin  B. Spectroscopy
3. Acetylcholine
4. GABA
5. Glutamate
Tools

- Behavior
- Pharmacology - drug effects
  - Increase - agonists
  - Decrease - antagonists
- Receptor location
- Anatomical connections
- Molecular characterization
Synapse - sites of action

Siegel et al,
Basic Neurochemistry
Sixth edition
Fast Receptor

Kandel et al, Principles of Neural Science
Slow Receptor

Influences activity on scale of minutes to days

Kandel et al, Principles of Neural Science, 3rd edition
Brain Anatomy and Function

- frontal cortex - higher cognition, planning
- brainstem - basic physiological functions
- striatum - motor
- limbic system - memory, emotion
- amygdala - fear
- nucleus accumbens - reward
- ventral tegmental area - reward

Kandel et al, Principles of Neural Science, 3rd edition
Receptors

Classified through:
• drug related characteristics
• intracellular signal-transduction mechanisms
• amino acid sequence of receptor protein
## Dopamine receptors

<table>
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<tr>
<th>Effector</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
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<td>cAMP</td>
<td>cAMP</td>
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</table>
DOPAMINE (DA)

- ventral tegmentum, nucleus acumbens
- frontal cortex
- mesolimbic
- striatum
COMT - effects of polymorphism

- COMT metabolizes DA
- LESS DA, poorer prefrontal performance
- Met allele is LESS active than val allele, MORE DA

Egan et al, PNAS, 2001
Parkinson’s Disease

• Progressive neurodegenerative disorder
• DA containing neurons in substantia nigra
• Motor symptoms-incapacitating
• Cognitive and emotional symptoms
• Incidence - 0.5%
• Palliative treatment
  – drugs
  – surgery, DBS, fetal tissue, stem cell
Michael J. Fox

The Michael J. Fox Foundation for Parkinson’s Research is dedicated to ensuring the development of a cure for Parkinson’s disease within this decade through an aggressively funded research agenda.
Schizophrenia

- Illness which affects reality testing, motivation, social interaction
- Onset in early adulthood, lifetime illness
- Incidence 1% of population
- Genetics
  - Monozygotic twins, 50% concordance
  - First degree relatives, 12%
- Some symptoms reduced by medication
- No cure
Schizophrenia

- Dopamine hypothesis
- Other NT systems are important
OWN THE AWARDS EDITION VIDEO OR 2-DISC DVD JUNE 25th

BEST PICTURE
BRIAN GRAZER - RON HOWARD

BEST DIRECTOR
RON HOWARD

BEST SUPPORTING ACTRESS
JENNIFER CONNELLY

BEST SCREENPLAY
AKIVA GOLDSMAN
John Forbes Nash, Jr.

Nobel Laureate, Economics, 1993
DA Pharmacology

• Increase activity
  – L-dopa - increase amount of DA
  – cocaine - release
  – amphetamine - reduce uptake

• Decrease activity
  – haloperidol - block receptor
5-HT neurons along midline in brainstem
Projections to all areas of brain
Modulatory role?
Sero
tonin Receptors in CNS

5-HT\_1\textsubscript{[A,D,E,F]}

5-HT\_2\textsubscript{[A,B,C]}

5-HT\_3

5-HT\_4

5-HT\_5\textsubscript{[A,B]}

5-h\textsubscript{t}\_6

5-HT\_7
<table>
<thead>
<tr>
<th>5-HT₁</th>
<th>5-HT1A</th>
<th>limbic system</th>
<th>modulation of emotion</th>
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<td>neocortex</td>
<td>cognition</td>
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<tr>
<td>5-HT1D</td>
<td>basal ganglia</td>
<td>Parkinson’s disease</td>
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5-HT$_2$

Lack of selective agonists and antagonists hampers determining functional role

| 5-HT2A | frontal cortex |
|        | basal ganglia  |
|        | olfactory nuclei |

| 5-HT2C | limbic system |
|        | neocortex   |
|        | basal ganglia |
5-HT$_3$

5-HT3 medulla pain
neocortex
limbic system
area postrema chemoreceptor trigger zone

facilitate release of substance P
modulate DA release in VTA
Serotonin Effects

- Appetitive
- Emotional
- Motor
- Cognition
- Autonomic
- Endocrine
- Circadian
Depression

- Selective serotonin reuptake inhibitors
- fluoxetine (Prozac)
Appetitive

- D-fenfluramine
- promotes release of 5-HT
- reuptake inhibitor
- reduces meal size, rate of eating and eating between meals
Synapse - sites of action
Acetylcholine (ACh)

- ACh found in bacteria, fungi and protozoa and plants
- Have biosynthetic and degradative capacities
- ACh is distributed outside of the nervous system:
  - cornea
  - ciliated epithelia
  - placenta
Acetylcholine Receptor

NICOTINIC  Neuromuscular
MUSCARINIC
M1  hippocampus
cerebral cortex
M2  cerebellum
brainstem
M4  striatum
ACh - Neuromuscular

- Botulinum is a neurotoxin produced by the gram positive bacterium Clostridium botulinum
- Interferes with presynaptic ACh release
- Denervates muscle
Myasthenia Gravis

• abnormal muscle fatigability
• muscle shows evidence of inflammation
• autoimmune process - ACh receptor
Acetylcholinesterase

- Acetylcholine is broken down by acetylcholinesterases (AChE)
- AChE inhibitors interfere with AChE, prolonging the action of ACh
- Reversible AChE have been used clinically
Myasthenia Gravis
Alzheimer’s Disease

- Cholinergic neurons observed to die out
- Cholinergic antagonists observed to impair memory
- Pharmacological strategy to prolong action of acetylcholine
**Figure 2.** Mean (± SEM) Clinician’s Interview–Based Impression of Change including caregiver information (CIBIC plus) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 455 were included in the intention-to-treat analysis at end point.
Acetylcholinesterase

- Build-up of ACh at cholinergic synapses can be toxic
- Organophosphorus or nerve gases, form incredibly stable phosphorus bonds with AChE.
- Irreversible AChE inhibitors are highly toxic.
Tabun

Used by Iraq in 1980 war with Iran
Exposure to 1 mg
• felt first in the eyes (as a persistent contraction of the pupil)
• chest (as a tightness or asthma-like constriction)
• running nose, sweating
• involuntary urination and defaecation
• vomiting, twitching
• convulsions, paralysis and unconsciousness
Sarin - 20 March 1995

- Sarin released in Tokyo subway during rush hour
- 12 fatalities, 5500 injured
- Police are paramedics
- Large stocks of antidote
- Poison not vaporized
GABA (gamma-aminobutyric acid)

• major inhibitor neurotransmitter in mammalian CNS
• ubiquitous in the brain
• found in millimolar quantities (unlike DA micromolar)
GABA Receptors

- $\text{GABA}_A$
  - Cl- channel
  - membrane hyperpolarization
  - many different isoforms

- $\text{GABA}_B$
  - K+ channels
  - decrease Ca2++ conductance
GABA pharmacology

- Barbiturates
- Benzodiazepine
- Ethanol
- Steroid

Siegel et al,
Basic Neurochemistry
Sixth edition
GABA disease

- epilepsy
- alcoholism
- Huntington’s disease
- tardive dyskinesia
- schizophrenia
- sleep disorders
- Parkinson’s disease
- mental retardation
Glutamate

- Major excitatory neurotransmitter
- A neurotoxin when energy metabolism is compromised
Glutamate receptors

• Ionotropic (ion channels)
  – NMDA
  – AMPA
  – Kainate

• Metabotropic (second messenger systems)
  – Class I
  – Class II
  – Class III
Cascade

Siegel et al,
Basic Neurochemistry
Sixth edition
Paths to Neuronal Injury

- Clinical trials have been disappointing
NMDA

- Phencyclidine
- Developed after WWI as surgical anesthetic - not safe
- 1957 - Sernyl, Parke-Davis tests as anesthetic, side effects of hallucinations, delirium
- 1965 - Sernylan - marketed as an animal tranquilizer
- Appeared on street, produces syndrome similar to schizophrenia
- PCP binds to the NMDA receptor
Neurolathyrisism

• lower limb weakness
• epidemics with droughts
• India, sub Sahara
Grasspea (Lathyrus sativus)

- Hippocrates described a paralysis associated with eating peas
- Plant resistant to drought, used to feed animals
- produces a legume similar to mung bean
- OK to eat in small quantities
Neurolathyrysm

• Get weakness in 2-3 weeks
• Paralysis in 3-6 months
• Mental retardation and death in children
• Men > Women
β-ODAP

3-(N-oxalyl)-L-2,3-diaminopropionic acid (β-ODAP) (Spencer et al., 1986 and Roy and Spencer, 1989)

Active at AMPA receptors

Damages motor neurons in specific region of spinal cord controlling the leg musculature
Grasspea (Lathyrus sativus)

- Outlawed in some countries but continues to be grown
- New strains produced through cross breeding which reduces neurotoxin from 1.2% to .02%
- Implications for other degenerative disorders

International Center for Agricultural Research in the Dry Areas (ICARDA)
Top Drug Categories by Sales (2000)

• 1 Cholesterol reducers statins
• 2 SSRI
• 3 Proton pump inhibitors
• 4 Cytostatics
• 5 Calcium blockers
• 6 Antipsychotics
• 7 Erythropoetins
• 8 COX-2 inhibitors
• 9 Anti seizure
• 10 ACE inhibitors

Pharmacy Times
Top Drug Categories by Scripts (2000)

- 1 Codeine 103M
- 2 Aminopenicillins 53M
- 3 SSRI/SNRI 42M
- ...
- 7 Benzodiazepines 39M
- ...
- 14 Anti seizure 26M

Pharmacy Times
MR Techniques

Direct measurement

Indirect measurement
GABA Measurement

Fig. 4. GABA-edited spectra measured in an epileptic subject before and during vigabatrin administration. Spectra: lower, before vigabatrin; upper, during treatment with 4 g per day of vigabatrin. The intensity of the edited C4 GABA resonance at 3.0 ppm (GABA-4CH₂) is increased by 2.3 times over the intensity in the spectrum obtained before vigabatrin administration.

Fig. 5. The GABA concentration measured in the occipital lobe of control and epileptic subjects plotted versus vigabatrin dosage. □, Eight measurements on four control subjects (mean 1.1 ± 0.1 μmol/cm² of brain); ■ and ●, two epileptic subjects from which multiple measurements were obtained; ▲ and ▼, measurements obtained from separate epileptic subjects. A general increase in GABA concentration with vigabatrin dosage was observed.

Rothman et al, PNAS, 1993
Anticonvulsant comparison

- Drugs have different mechanisms
  - topiramate - potentiates GABA action
  - gabapentin - structurally like GABA but not an agonist, no inhibition of degradation
  - lamotrigine - inhibit Na+, modulate excitatory NT release

- Use MRS to examine acute and chronic effects on healthy subjects
Anticonvulsant comparison

- Healthy subjects given drug and followed both acutely and chronically (4 weeks) with MRS at 4.1T

<table>
<thead>
<tr>
<th></th>
<th>ACUTE</th>
<th>CHRONIC</th>
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<tbody>
<tr>
<td>Topiramate</td>
<td>70%</td>
<td>46%</td>
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<tr>
<td>Gabapentin</td>
<td>48%</td>
<td>25%</td>
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<tr>
<td>Lamotrigine</td>
<td>0%</td>
<td>25%</td>
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</tbody>
</table>

Kuzniecky et al., Neurology, 2002
Glu, Gln at 4.0T

STEAM acquisition, 8cc anterior cingulate, CMRR, University of Minnesota
Glutamate/Glutamine

- Glutamate/glutamine cycling
- Can use C-13 MRS to monitor and quantitate flux rates.
Indirect Measurement

- Parkinson’s disease - fetal cell transplant
- PET - typically used for DA receptor
- PET - radiation complicates longitudinal studies
- Use MR to assess blood flow response to drug challenge
- Generalized or specific response?
- Role for MR?
phMRI

Chen et al, Neuroreport, 1999
Fetal cell transplant monitoring

Chen et al, Neuroreport, 1999
# POST TEST:
Match the NT to the behavior

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POST TEST:
Match the NT to a drug

1. Dopamine  
2. Serotonin  
3. Acetylcholine  
4. GABA  
5. Glutamate  

A. diazepam (Valium)  
B. donepezil (Aricept)  
C. Phencyclidine  
D. fluoxetine (Prozac)  
E. Cocaine
POST TEST:
Match the NT to the MR method

1. Dopamine  
2. Serotonin  
3. Acetylcholine  
4. GABA  
5. Glutamate

A. BOLD  
B. Spectroscopy
SLIDES

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