ISMRM Weekend Educational Course on Basics of Brain Function
May 18, 2002, Honolulu, Hawaii

Basics of Behavioral Neurochemistry

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SLIDES

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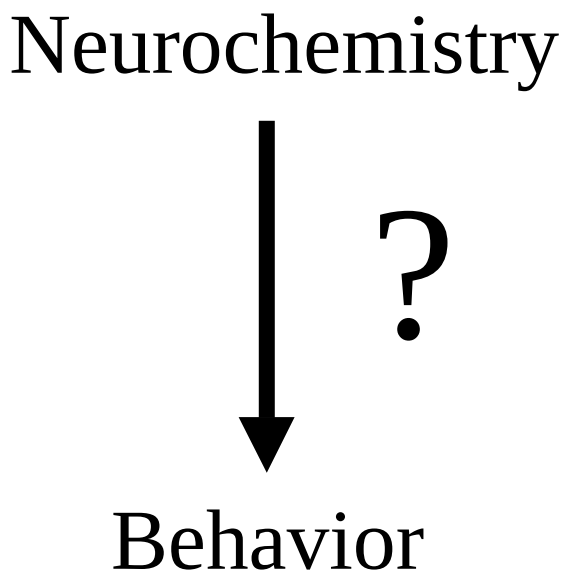

Neurochemistry
?
Behavior

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

A. Alzheimer’s disease
B. epilepsy
C. depression
D. Schizophrenia
E. Parkinson’s disease

PRETEST:
Match the NT to a drug

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

A. diazepam (Valium)
B. donepezil (Aricept)
C. Phencylidine
D. fluoxetine (Prozac)
E. Cocaine

PRETEST:
Match the NT to the MR method

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

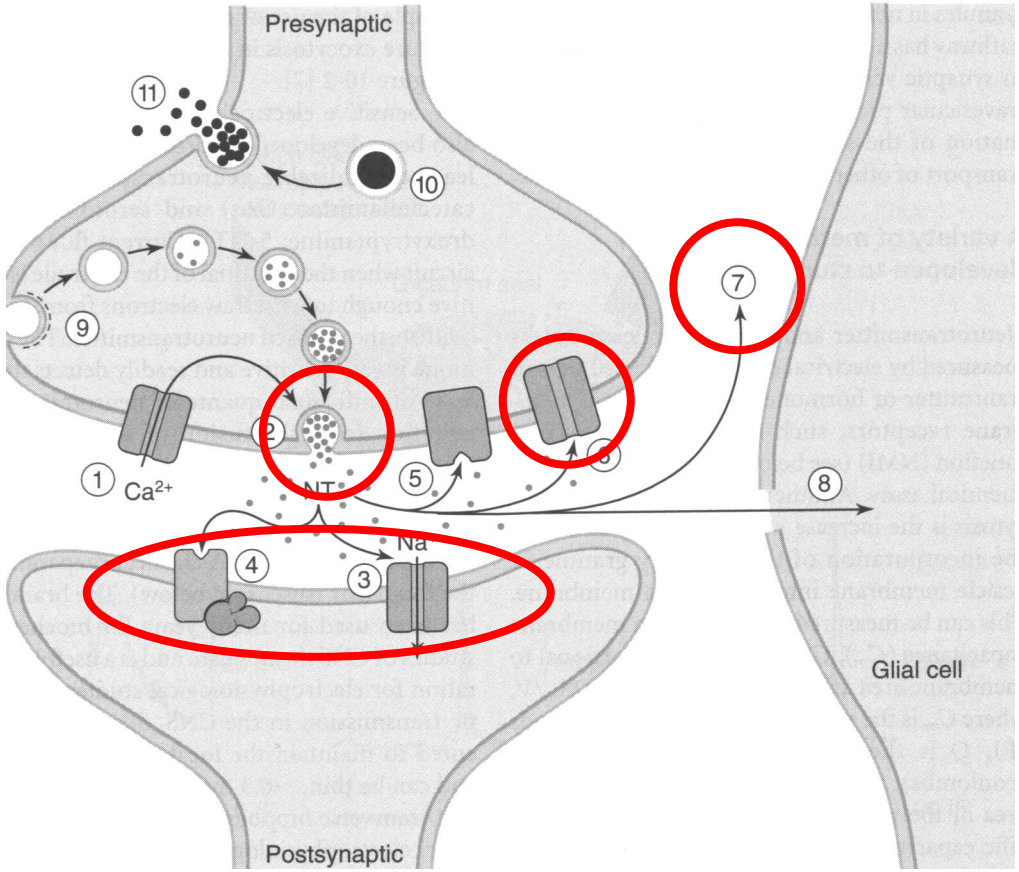
A. BOLD

B. Spectroscopy

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

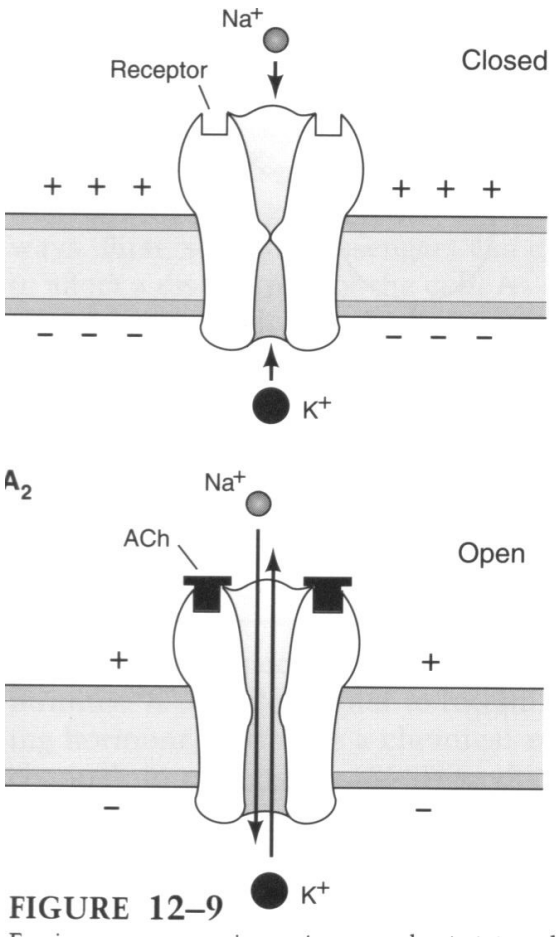
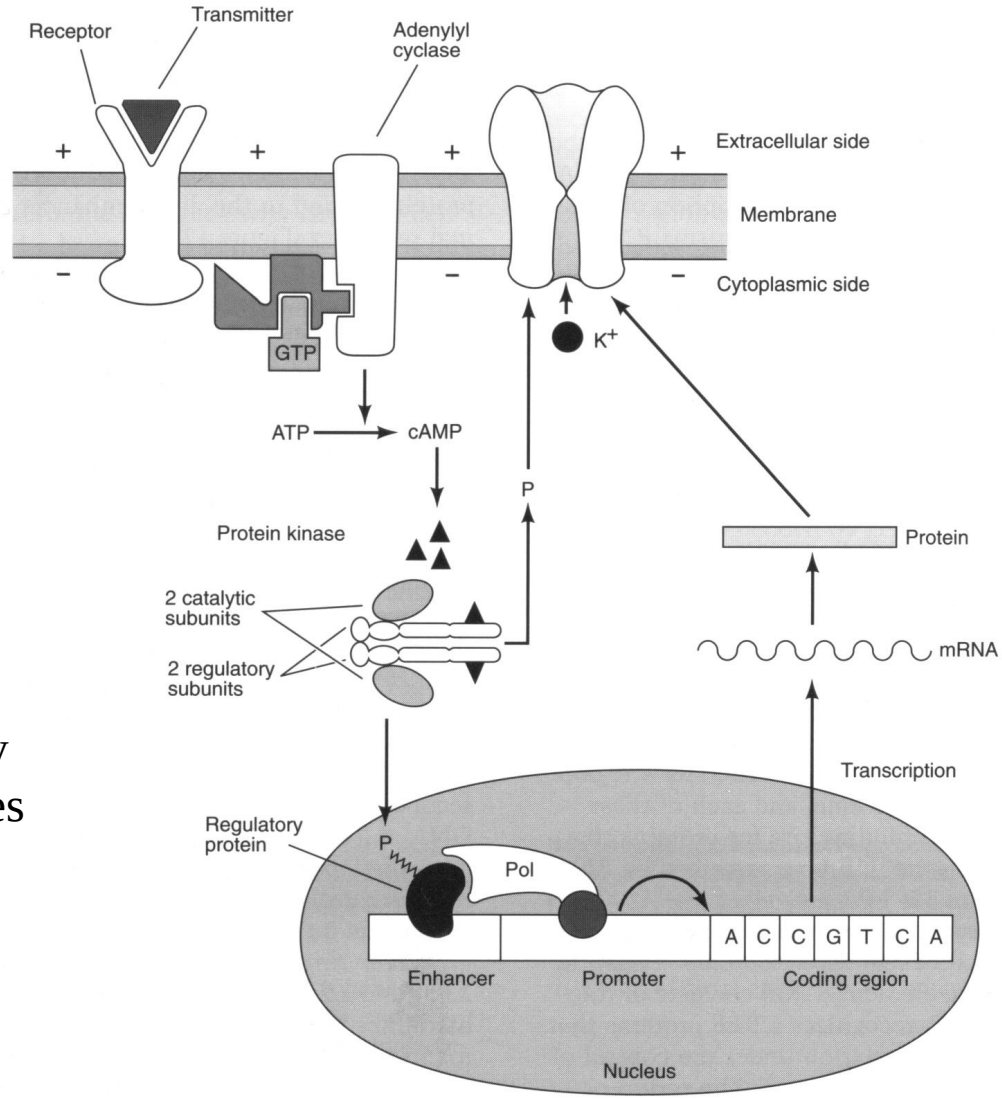


FIGURE 12–9

Kandel et al, Principles of Neural Science

Slow Receptor

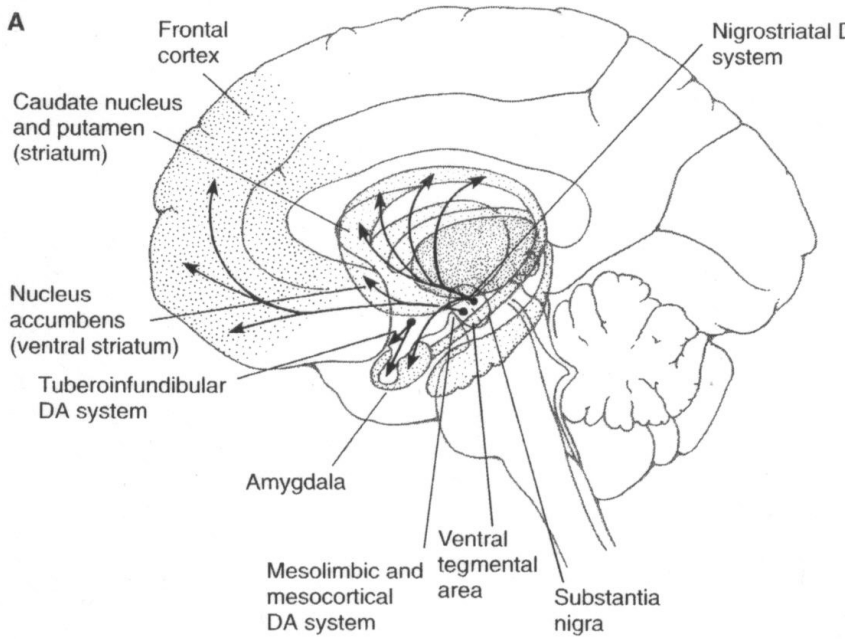


Influences activity on scale of minutes to days

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 acumbens - 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

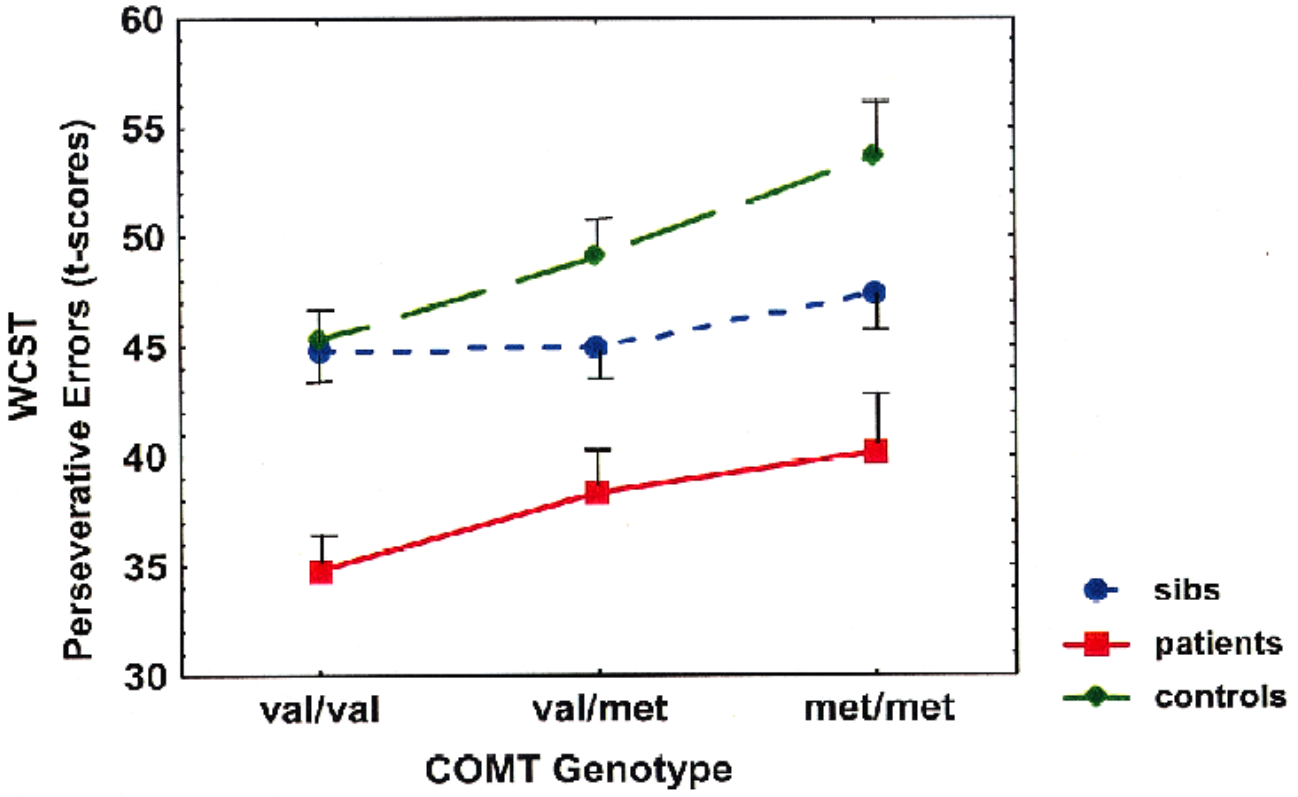
	D1	D2	D3	D4	D5
AA	446	415	400	387	477
Chro	5	11	3	11	4
mRNA	CP	hippo	CP	hypoth	frontal
	NA	hypoth	NA	NA	medulla
	OT		OT	OT	midbrain
effector	cAMP	cAMP	cAMP	cAMP	cAMP
			K,Ca		K

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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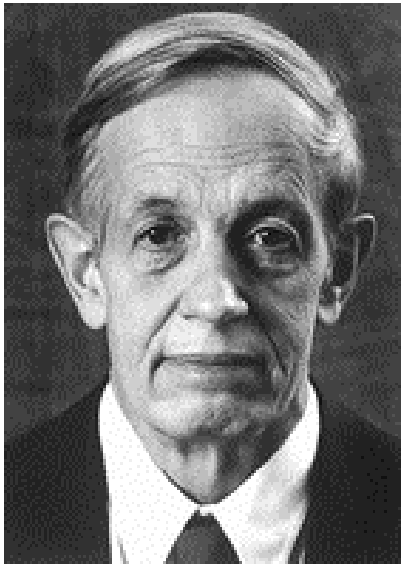
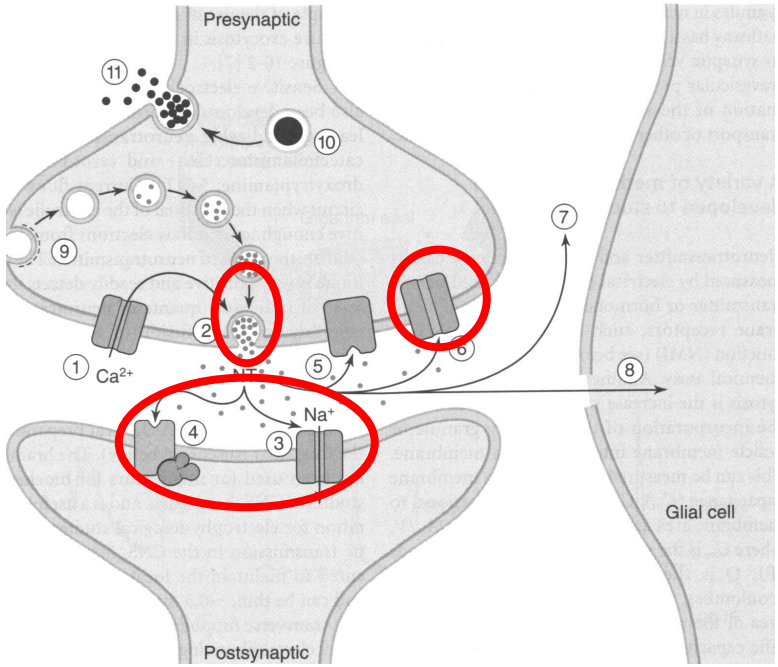


Nobel Laureate, Economics, 1993

DA Pharmacology

- Increase activity
  - L-dopa - increase amount of DA
  - cocaine - release
  - amphetamine - reduce uptake
- Decrease activity
  - haloperidol - block receptor



SEROTONIN (5-HT)

5-HT neurons along midline in brainstem
Projections to all areas of brain
Modulatory role?

Serotonin Receptors in CNS

$5\text{-}HT_{1[A,D,E,F]}$

$5\text{-}HT_{2[A,B,C]}$

$5\text{-}HT_{3}$

$5\text{-}HT_{4}$

$5\text{-}HT_{5[A,B]}$

$5\text{-}ht_{6}$

$5\text{-}HT_{7}$

5-HT_1

5-HT1A	limbic system	modulation of emotion
	neocortex	cognition
5-HT1D	basal ganglia	Parkinson’s disease

$5\text{-}HT_2$

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

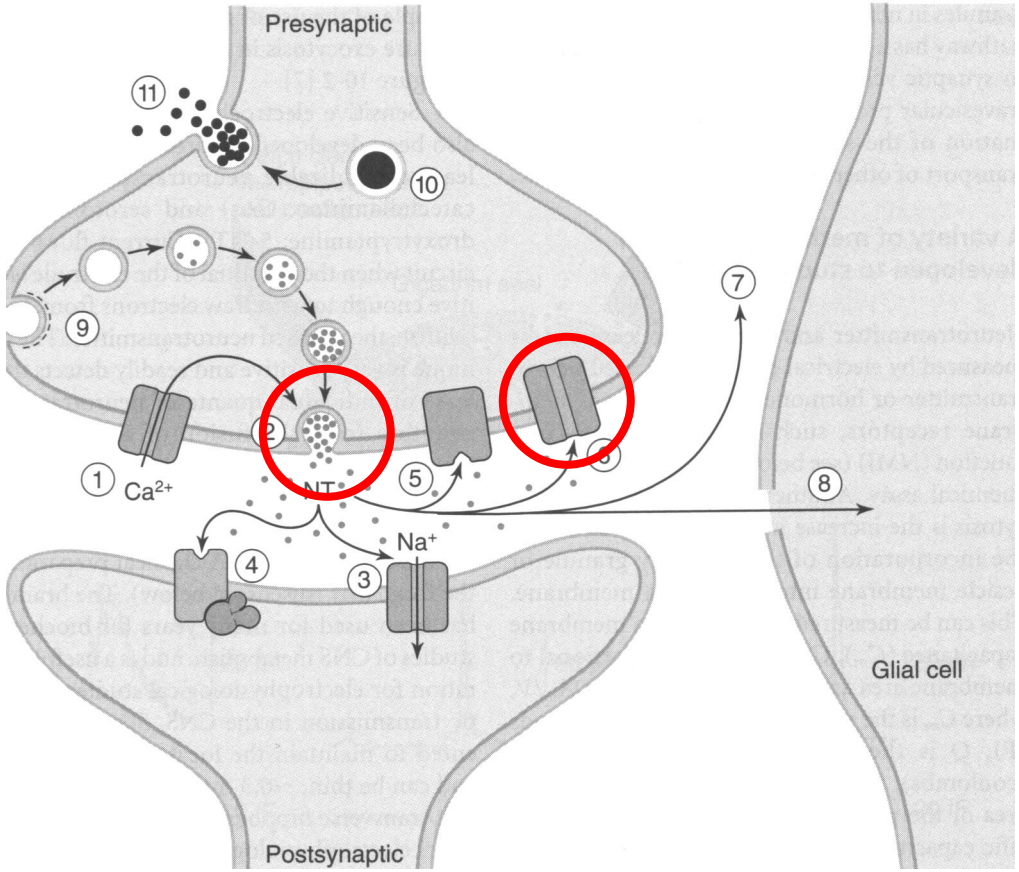
Depression

- 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



Siegel et al,
Basic Neurochemistry

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

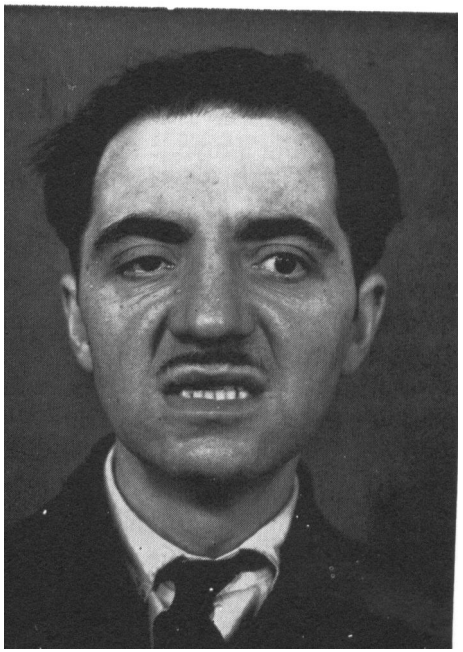
NICOTINIC	Neuromuscular
MUSCARINIC	
M1	hippocampus
	cerebral cortex
M2	cerebellum
	brainstem
M4	striatum

ACh - Neuromuscular

- Botulinum is a neurotoxin produced by the gram positive bacterium Clostridium botulinum
- Interferes with pre-synaptic ACh release
- Denervates muscle

Myasthenia Gravis

- abnormal muscle fatigabiltiy
- muscle shows evidence of inflammation
- autoimmune process - ACh receptor



Brain's Clinical Neurology
Fifth edition

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

Brain's Clinical Neurology
Fifth edition

Alzheimer’s Disease

- Cholinergic neurons observed to die out
- Cholinergic antagonists observed to impair memory
- Pharmacological strategy to prolong action of acetylcholine

AD treatment - donepezil

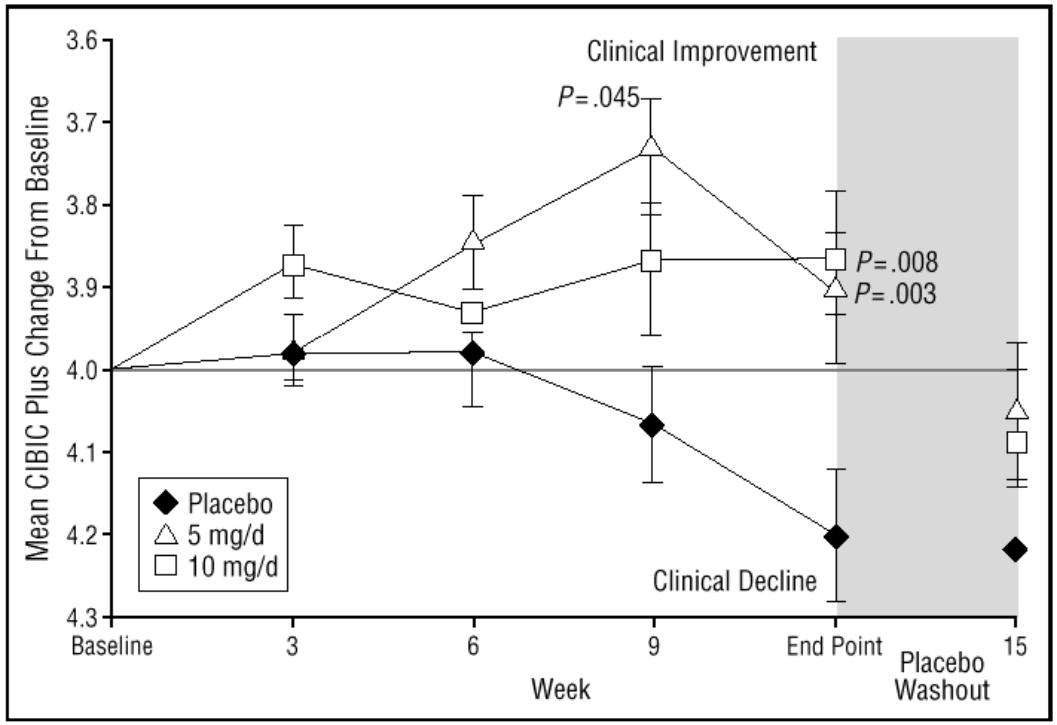


Figure 2. *Mean (± SEM) Clinician's Interview–Based Impression of Change including caregiver information (CIBIC plus) scores for patients with mild to moderately severe Alzheimer disease receiving 5 mg/d and 10 mg/d of donepezil hydrochloride and placebo. Of the 468 patients randomized to receive treatment, 455 were included in the intention-to-treat analysis at end point.*

Rogers et al, Arch Int Med, 1998.

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 - 20March1995

- 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)

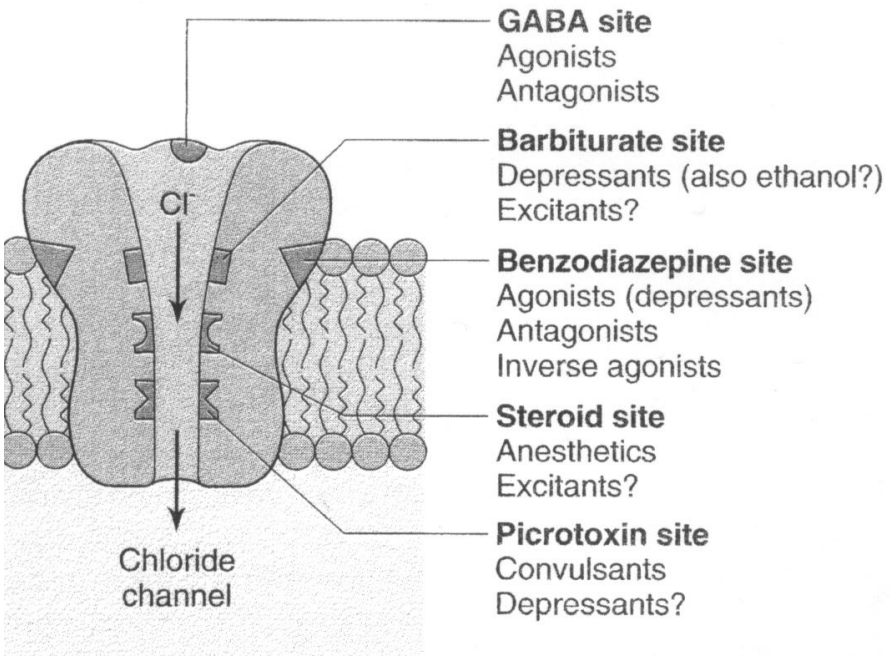
- major inhibitor neurotransmitter in mammalian CNS
- ubiquitous in the brain
- found in millimolar quantities (unlike DA micromolar)

GABA Receptors

- $GABA_A$
  - Cl- channel
  - membrane hyperpolarization
  - many different isoforms
- $GABA_B$
  - 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

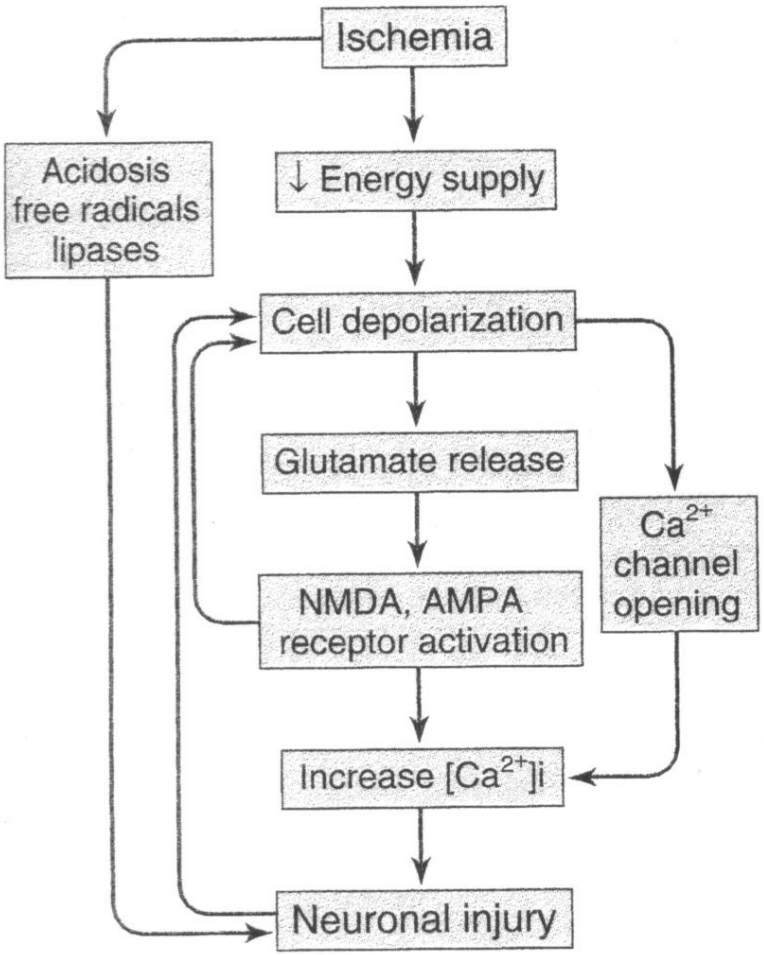
Glutamate

- 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
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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

Neurolathyrism

- 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

Neurolathyrism

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

ß-ODAP

3-(N-oxalyl)-L-2,3-diaminopropionic acid (ß-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

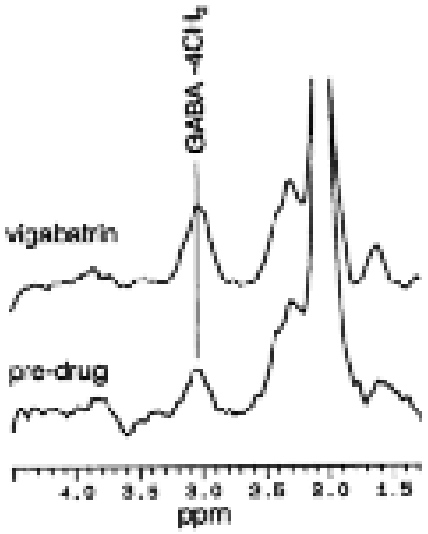


FIG. 4. GABA edited spectra measured in an epileptic subject before and during vigabatrin administration. Spectra: lower, before vigabatrin; upper, during treatment with 4 g per day of vigabatrin. The intensity of the edited C4 GABA resonance at 3.0 ppm (GABA-$4CH_2$) is increased by 2.3 times over the intensity in the spectrum obtained before vigabatrin administration.

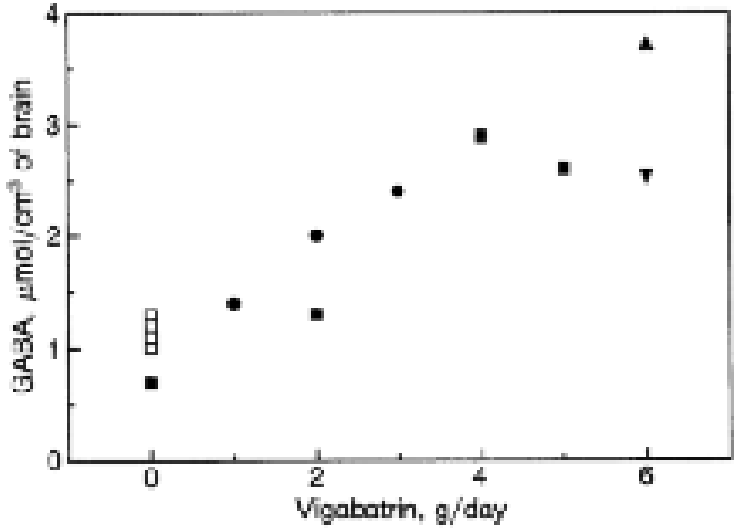


FIG. 5. The GABA concentration measured in the occipital lobe of control and epileptic subjects plotted versus vigabatrin dosage. □, Eight measurements on four control subjects (mean 1.1 ± 0.1 μmol/cm³ of brain); ■ and ●, two epileptic subjects from which multiple measurements were obtained; ▲ and ▼, 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

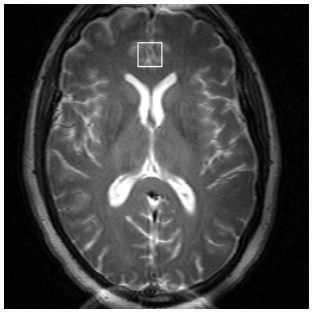
Anticonvulsant comparison

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

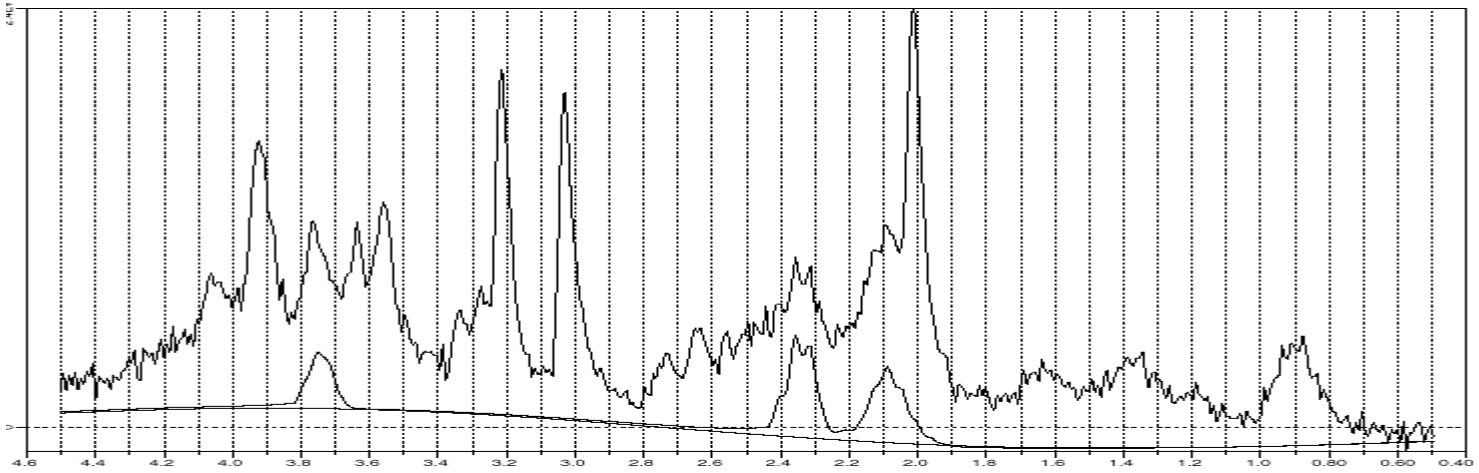
	ACUTE	CHRONIC
Topiramate	70%	46%
Gabapentin	48%	25%
Lamotrigine	0%	25%

Kuzniecky et al., Neurology, 2002

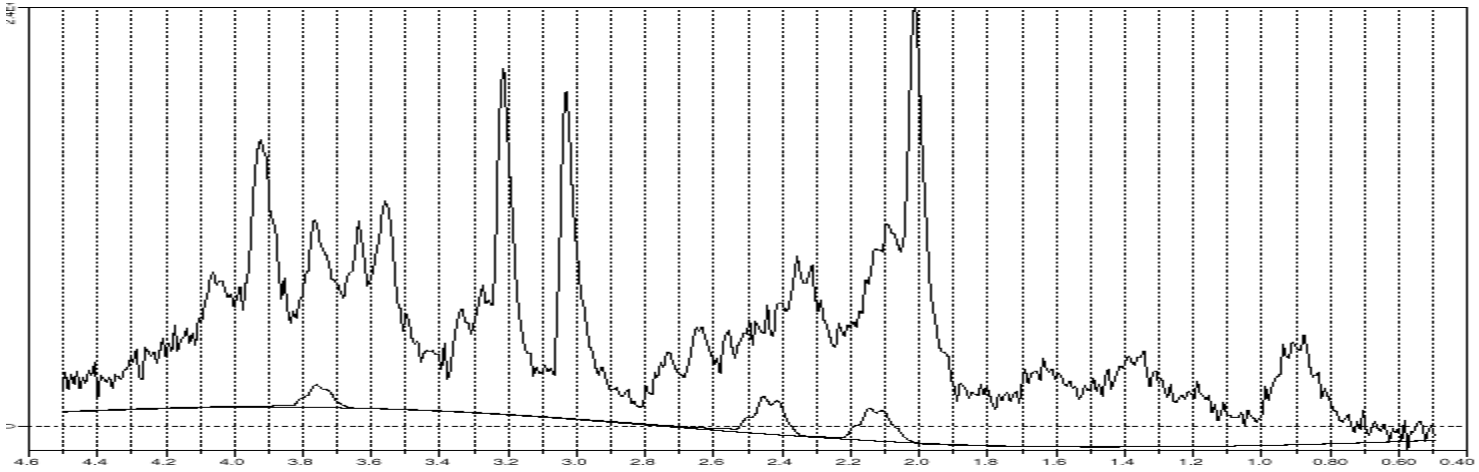
Glu, Gln at 4.0T



Glu



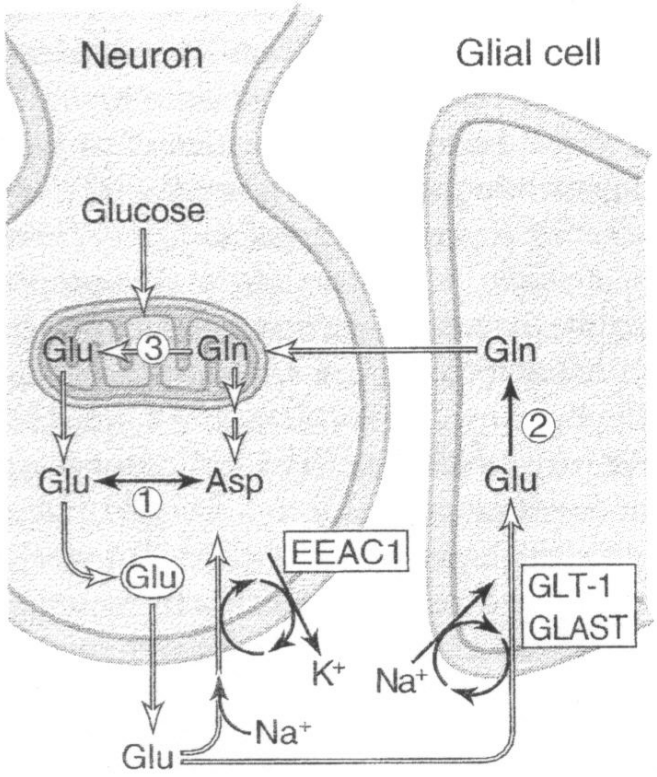
Gln



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.

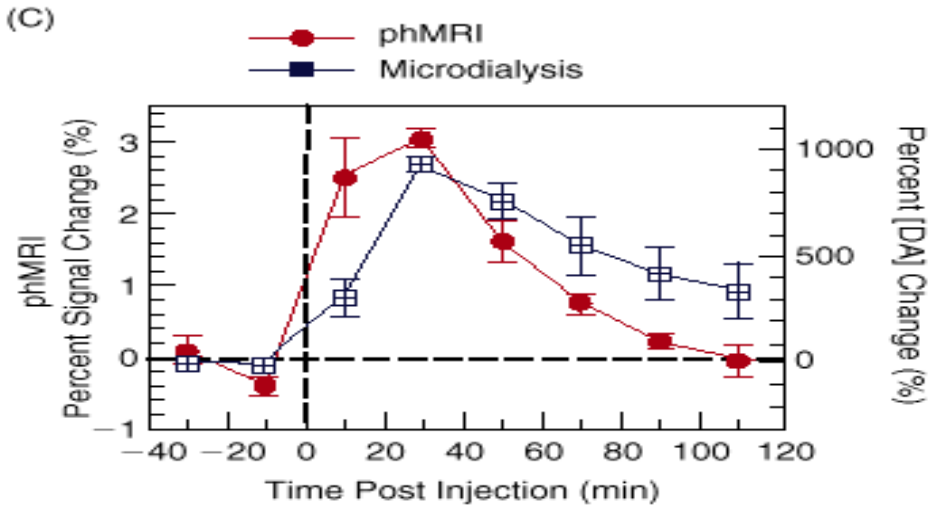


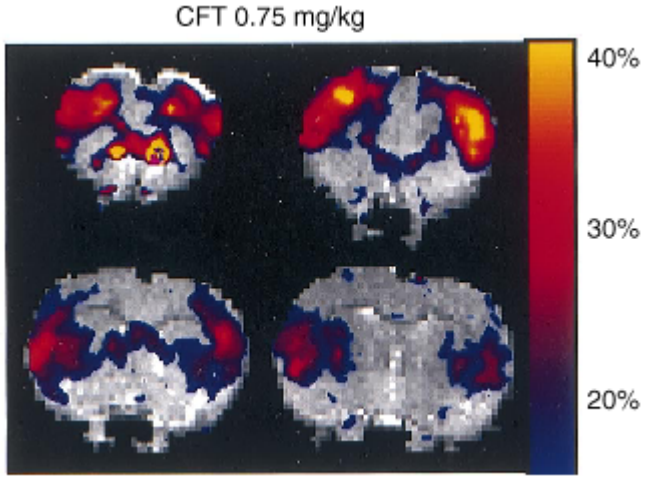
Siegel et al,
Basic Neurochemistry
Sixth edition

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?

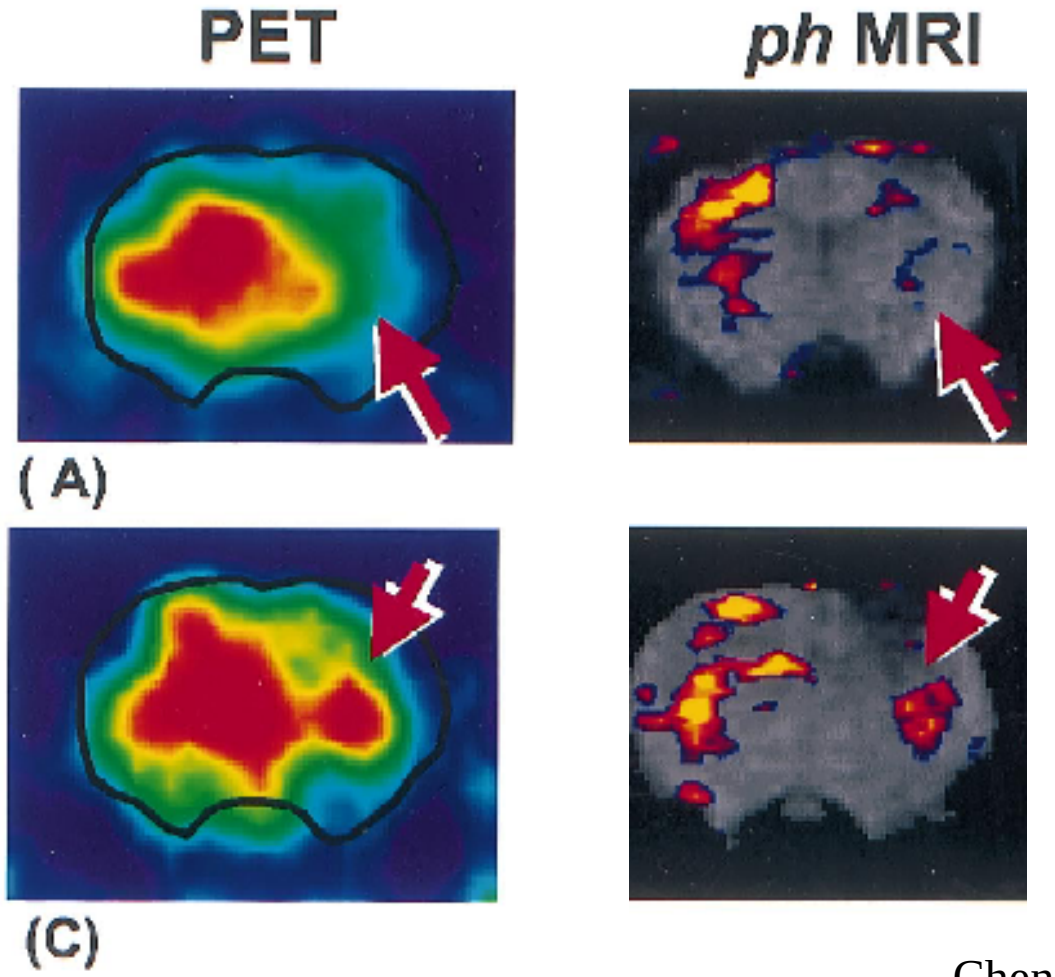
phMRI





Chen et al, Neuroreport, 1999

Fetal cell transplant monitoring



Chen et al, Neuroreport, 1999

POST TEST:
Match the NT to the behavior

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

A. Alzheimer’s disease
B. epilepsy
C. depression
D. Schizophrenia
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POST TEST:
Match the NT to a drug

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2. Serotonin
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5. Glutamate

A. diazepam (Valium)
B. donepezil (Aricept)
C. Phencylidine
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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