Neurotransmitters
Biochemistry of synapses

- Synaptosomes
- gentle homogenization
- pre- and post-synaptic membranes stick
- membranes seal back up
- all the chemicals of the synapse can thus be found in one centrifuge tube layer.
(1) Presynaptic terminal

(2) Action potential

(3) Application of transmitter, agonists, or antagonists
Criteria, pharmacology

• used to be real stringent
• Now (1) presence, (2) release & (3) receptors
• "putative neurotransmitter" to cast doubt
• Pharmacology was pivotal
• agonist - a drug that mimics the neurotransmitter
• antagonist - a drug that blocks the neurotransmitter
### TABLE 6.1
**Functional Features of the Major Neurotransmitters (Part 1)**

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<th>Neurotransmitter</th>
<th>Postsynaptic effect$^a$</th>
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<td>AChEase</td>
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<td>Excitatory</td>
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<td>Glutaminase</td>
<td>Transporters</td>
<td>Small, clear</td>
</tr>
<tr>
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<td>Inhibitory</td>
<td>Glutamate</td>
<td>GAD</td>
<td>Transporters</td>
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</tr>
<tr>
<td>Glycine</td>
<td>Inhibitory</td>
<td>Serine</td>
<td>Phosphoserine</td>
<td>Transporters</td>
<td>Small, clear</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Excitatory</td>
<td>Tyrosine</td>
<td>Tyrosine hydroxylase</td>
<td>Transporters, MAO, COMT</td>
<td>Small dense-core, or large irregular dense-core</td>
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$^a$The most common postsynaptic effect is indicated; the same transmitter can elicit postsynaptic excitation or inhibition depending on the nature of the ion channels affected by transmitter binding (see Chapter 7).
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<tr>
<th>Neurotransmitter</th>
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<th>Rate-limiting step in synthesis</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (5-HT)</td>
<td>Excitatory</td>
<td>Tryptophan</td>
<td>Tryptophan hydroxylase</td>
<td>Transporters, MAO</td>
<td>Large, dense-core</td>
</tr>
<tr>
<td>Histamine</td>
<td>Excitatory</td>
<td>Histidine</td>
<td>Histidine decarboxylase</td>
<td>Transporters</td>
<td>Large, dense-core</td>
</tr>
<tr>
<td>ATP</td>
<td>Excitatory</td>
<td>ADP</td>
<td>Mitochondrial oxidative</td>
<td>Hydrolysis to AMP and adenosine</td>
<td>Small, clear</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>phosphorylation; glycolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>Excitatory and inhibitory</td>
<td>Amino acids (protein synthesis)</td>
<td>Synthesis and transport</td>
<td>Proteases</td>
<td>Large, dense-core</td>
</tr>
<tr>
<td>Endocannabinoids</td>
<td>Inhibits inhibition</td>
<td>Membrane lipids</td>
<td>Enzymatic modification of lipids</td>
<td>Hydrolasis by FAAH</td>
<td>None</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Excitatory and inhibitory</td>
<td>Arginine</td>
<td>Nitric oxide synthase</td>
<td>Spontaneous oxidation</td>
<td>None</td>
</tr>
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\(^d\)The most common postsynaptic effect is indicated; the same transmitter can elicit postsynaptic excitation or inhibition depending on the nature of the ion channels affected by transmitter binding (see Chapter 7).
SMALL-MOLECULE NEUROTRANSMITTERS

**Acetylcholine**
\[(\text{CH}_3)_3\text{N}^+ - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{C} - \text{CH}_3\]

**AMINO ACIDS**

- **Glutamate**
  \[\text{H}_3\text{N}^+ - \text{C} - \text{COO}^-\]
  \[\text{CH}_2\]
  \[\text{CH}_2\]
  \[\text{COOH}\]

- **Aspartate**
  \[\text{H}_3\text{N}^+ - \text{C} - \text{COO}^-\]
  \[\text{CH}_2\]
  \[\text{COOH}\]

- **GABA**
  \[\text{H}_3\text{N}^+ - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{COO}^-\]

- **Glycine**
  \[\text{H}_3\text{N}^+ - \text{C} - \text{COO}^-\]
  \[\text{H}\]
SMALL-MOLECULE NEUROTRANSMITTERS

PURINES

ATP

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O}^- & \quad \text{O}^- \\
\text{O}^- & \quad \text{O}^- \\
\text{O}^- & \quad \text{O}^- \\
\text{O}^- & \quad \text{O}^- \\
\text{CH}_2 & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{OH} & \quad \text{OH} \\
\text{NH}_2 & \quad \text{N} \\
\text{N} & \quad \text{N}
\end{align*}
\]
SMALL-MOLECULE NEUROTRANSMITTERS

BIOGENIC AMINES

CATECHOLAMINES

Dopamine

\[
\text{HO} \quad \text{CH}_2 \cdot \text{CH}_2 \cdot \overset{+}{\text{NH}_3}
\]

\[
\text{OH} \quad \text{OH}
\]

Norepinephrine

\[
\text{CH}_2 \cdot \text{CH}_2 \cdot \overset{+}{\text{NH}_3}
\]

\[
\text{OH} \quad \text{OH} \quad \text{HO}
\]

Epinephrine

\[
\text{CH}_2 \cdot \text{CH}_2 \cdot \overset{+}{\text{NH}_2}
\]

\[
\text{CH}_3 \quad \text{HO} \quad \text{OH}
\]
SMALL-MOLECULE NEUROTRANSMITTERS

BIOGENIC AMINES

INDOLEAMINE
Serotonin (5-HT)

IMIDAZOLEAMINE
Histamine
Example: Methionine enkephalin (Tyr–Gly–Gly–Phe–Met)
Monamines (acetylcholine, catecholamines, serotonin, histamine, octopamine)
Amino Acids (GABA [gamma amino butyric acid], glutamate, glycine)
Peptides (many)
Gasses like Nitric Oxide (NO)
Purines - ATP (and AMP and adenosine) excitatory transmitters (not much to say)
endocannabinoids
(A) Brain-gut peptides

- Substance P: Asp-Val-Leu-Arg-Pro-Glu-Arg-Glu
- Cholecystokinin octapeptide: Asp-Tyr-Met-Glu-Arg-Arg-Val-Arg
- Vasoactive intestinal peptide: His-Pro-Ala-Val-Asp-Thr-Glu-Trp-Leu-Arg-Leu-Arg-Thr-Asp-Arg-Asp

(B) Opioid peptides

- Leucine enkephalin: Tyr-Glu-Phen
- α-Endorphin: Tyr-Glu-Phen-Val-Glu-Glu-Lys-Thr-Leu-Val-Asp-Val-Thr
- Dynorphin A: Tyr-Glu-Phen-Leu-Glu-Glu-Leu-Pro-Leu-Val-Leu-Val-Glu

(C) Pituitary peptides

- Vasopressin: Cycl-Phe-Glu-Lys-Cys-Glu-Cys-Glu-Cys-Glu
- Oxytocin: Cycl-Ile-Cys-Cys-Cys-Glu-Glu-Glu-Glu-Glu
- Adrenocorticotropic hormone: Ser-Arg-Val-Glu-His-Pro-Val-Glu-Asp-Val

(D) Hypothalamic-releasing peptides

- Thyrotropin releasing hormone: Glu-His-Pro
- Leutinizing hormone-releasing hormone: Glu-His-Thr-Asp-Tyr-Glu-Leu-Asp-Arg-Glu
- Somatostatin-14: Ala-Cys-Lys-Asp-Phen-Trp-Lys-Arg-Thr-Thr

(E) Miscellaneous peptides

- Angiotensin-II: Asp-Arg-Asp-Val-Tyr-Ile-Pro
- Neurotensin: Glu-Arg-Glu-Tyr-Leu-Arg-Pro-Ile-Asp

Amino acid properties

- Orange: Hydrophobic
- Green: Polar, uncharged
- Red: Acidic
- Blue: Basic

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Diffusion and degradation
synthesis for small molecules in terminal
enzyme transport - slow axonal transport
peptides are synthesized as pre-propeptides
in rough endoplasmic reticulum
signal sequence (for secretion) is removed
Propeptide is processed in Golgi apparatus,
put in vesicles, fast axonal transport using ATP and kinesin
Further processing, especially cleavage
(B)

Pre-propeptide

Signal peptide

Pre-proenkephalin A

Proenkephalin A

Propeptide

Active peptides

Met-enkephalin

Leu-enkephalin

Met-enkephalin
Notes from outline

- 40 nm (small) electron lucent vesicles
- somewhat larger dense core are catecholamines or peptides
- 100 nm diameter granules are secretory
- Importantly, transporters concentrate transmitters into vesicles
(A) ELECTRONIC SYNAPSE

- Presynaptic neuron
- Cytoplasm
- Mitochondrion
- Microtubule
- Gap junction
- Postsynaptic neuron

(B) CHEMICAL SYNAPSE

- Presynaptic neuron
- Synaptic vesicle
- Postsynaptic neuron
- Synaptic vesicle fusing
- Synaptic cleft
- Postsynaptic neurotransmitter receptor
- Postsynaptic membrane
(A) Ligand-gated ion channels

- Ions
- Neurotransmitter

Outside cell

Inside cell
(B) G-protein-coupled receptors

[Diagram showing the interaction between a neurotransmitter, receptor, effector protein, and ions.]
 Ionotropic vs Metabotropic

• Channels - ionotropic.
• Acetylcholine (cholinergic) nicotinic receptor
• Nicotine agonist, properties of antagonist
• G-protein-coupled receptor.
• Cholinergic muscarinic receptor
Stimulate vagus nerve of heart 1

Heart 1

Contraction force

Time (s)

Heart 2

Contraction force

Time (s)
Monamines, acetylcholine

- Loewi 1936 Nobel Prize (already covered)
- Reportedly, he thought of this experiment in a dream
- vagus-stuff slows heart (10th cranial nerve, parasympathetic)
Acetylcholine metabolism

- Dale 1936 Nobel "cholinergic" ("-ergic")
- unique in that amino acid not involved
- Dietary choline - reuptake or uptake (transporter is Na+ dependent)
- -> intraneural choline
- -Choline-O-acetyltransferase->
- H3-CO-O-CH2-N+-((CH3)3
- Acetyl Co-A is acetate donor
breakdown

- Acetylcholinesterase
- blocked by malathion and neostigmine
- organophosphates, nerve gas, etc
Axelrod

- 1970 Nobel
- Science
- Reflection
Tyrosine

\[
\begin{align*}
\text{Tyrosine} & \xrightarrow{\text{O}_2} \text{Tyrosine hydroxylase} \\
\text{Dihydroxyphenylalanine (DOPA)} & \xrightarrow{\text{DOPA decarboxylase}} \\
\text{Dopamine} & \xrightarrow{\text{O}_2} \text{Dopamine-\(\beta\) hydroxylase}
\end{align*}
\]

Norepinephrine

\[
\begin{align*}
\text{Norepinephrine} & \xrightarrow{\text{OH}} \text{Norepinephrine} \\
\text{Phenylethanolamine } N\text{-methyltransferase} & \xrightarrow{\text{RCH}_3} \\
\text{Epinephrine}
\end{align*}
\]
Norepinephrine (noradrenalin)

- tyrosine hydroxylase - rate limiting
- regulated by end-product inhibition
- calcium activates
- it is DOPA quinones which polymerase to make melanin
- substantia nigra is pale in Parkinson's
- => synthesis overlap
- DOPA decarboxylase - gets rid of l vs. d
- in insects, dopamine quinones "tan the hide"
more

- dopamine beta hydroxylase - adds optical asymetry back again
- interestingly, within vesicle
- ATP is released with NE, ATPase turns to adenosine
- Important agonists and antagonists and other drugs
- PNMT (phenolamine N-methyltraansferase)
- interestingly, in cytosol, necessitating transport out then in vesicle
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Metabolism (Axelrod)

- Most removal is by transporters, but there is breakdown
- MAO - monamine oxidase intracellular, inhibitors (MAOI's) are antidepressants
- on outer mitochondrial membrane
- COMT - catechol O-methyltransferase extracellular, but there are no inhibitors
- reuptake most important
Sympathetic division

- Superior cervical ganglion
- Constricts blood vessels
- Stellate ganglion
- Sympathetic ganglia
- Celiac ganglion
- Gallbladder
- Pancreas
- Liver
- Superior mesenteric ganglion
- Inferior mesenteric ganglion

Noradrenergic neurons
Postganglionic
Cholinergic neurons
Preganglionic
Postganglionic

Autonomic n.s.

- Motor system for smooth muscle and glands,
- acetylcholine and norepinephrine involvement
- Parasympathetic, cranio-sacral,
- ACh (nicotinic and muscarinic),
- ganglion near target
- Sympathetic, thoraco-lumbar,
- ACh (nicotinic) then NE,
- ganglion near spinal cord
• Many targets are "push-pull" like heart
• Some are unique like arterioles (sympathetic only) --
• close in peripheral vascular beds (make hands cold),
• open in muscle (hyperemia).
(B) Midbrain

Edinger-Westphal nucleus

Oculomotor nerve (III)

Upper medulla

Salivatory nuclei

Facial nerve (VII) and glossopharyngeal nerve (IX)

Middle medulla

Dorsal motor nucleus of vagus

Vagus nerve (X)

Nucleus ambiguus
Arrangement

• sympathetic output from lateral horn neuron -> white ramus -> sympathetic ganglion -> gray ramus
• Simpler for parasympathetic, i.e. from brain stem nucleus
• ...or ...lateral horn in sacral cord to parasympathetic ganglion
Enteric

- Contribution of neural network (plexus)
- to circular and longitudinal muscles
- to mediate peristalsis.
- Parasympathetic allows digestion,
- sympathetic puts it on hold.
- Atropine (I'll talk more about atropine in next outline) blocks muscarinic synapses and is in anti-diarrhea medications to slow motility.
Heart as an example

- Automaticity at SA and AV nodes
- (spread from myocardial cell to next myocardial cell).
- Sympathetic speeds heart,
- parasympathetic (via vagus, X) slows,
- and relaxed heart rate is slower than automatic rate.
A few years ago:

• "This is the only place where parasympathetic affects arterioles, dilating them in corpus cavernosum for erection. Sympathetic contributes to ejaculation."
Furchgott, Ignarro, Murad NO Nobel 1998

- adrenergic (via alpha 1 receptors) contracts smooth muscle,
- cholinergic (via muscarinic receptors) inhibits adrenergic-induced-contraction (resulting in relaxation);
- more than cholinergic and adrenergic, a little mentioned autonomic component, the NANC (nonadrenergic noncholinergic) system, mediates relaxation.
Something's gotta give

- Jack Nicholson has a heart attack while having sex, and the docs ask if he is on Viagra as they are about to give him nitroglycerine. (also listed in advertisements for ED (erectile dysfunction) medications because of interaction and resulting low blood pressure)
More on NO, ED, etc

- nitroglycerine for angina (chest pain)
- releases NO (nitric oxide) and relaxes the coronary arteries
- Nitric Oxide (NO), made by endothelial nitric oxide synthase (eNOS),
- unusual in that it diffuses across "postsynaptic" membrane
- to affect guanylyl cyclase (GC) involved in making cGMP.
Finally

- NO was endothelial derived relaxation factor (EDRF),
- mediator of parasympathetic nervous system's dilation of arterioles in corpus cavernosum.
- Viagra (sildenafil) inhibits the PDE that breaks down cGMP
Seroitonin

- = 5-HT (5-hydroxy tryptamine)
- tryptophan hydroxylase
- L-aromatic amino acid (5-HTP) decarboxylase
- Serotonin from Raphe nucleus is spread widely and involved in sleep (discussed later in the semester).
- Tryptophan in turkey blamed for sleepiness after Thanksgiving dinner.
SSRI’s

- (selective serotonin reuptake inhibitor)
- Prozac (fluoxetine)
- Paxil (paroxetine)
- Zoloft (sertraline)
- There is new controversy about whether these increase the incidence of suicide, now that they are given to teenagers,
- but there was also controversy over a decade ago.
- The other side of the argument is that it is given to depressed people.
Finally, (re Serotonin)

• LSD (lysergic acid diethylamide)
• agonist of 5HT receptors in Raphe,
• cause decreased output to brain (as in sleep).
• People used to take tryptophan, but bad batch caused eosinophilic-myalgia syndrome so FDA banned it in 1990.
Melatonin

• 2 more steps after 5-HT to make melatonin (sleep promoting hormone, higher at night)
• in pineal
• N-acetyltransferase (regulated) rate limiting and hydroxy indole O-methyl transferase.
• High at night, low during day, relates to biorhythms, see lecture later in the semester.
• In animals where light can reach the pineal, it has photoreceptors.
• For us, eye to suprachiasmatic nucleus of hypothalamus to pineal.
Finally (melatonin)

- Melatonin sales went wild in mid-1990's
- Books stated that melatonin was a "wonder," "miracle" or keeps you young
- Restore sleep cycle after jet lag.
- Controls reproduction - seasonal reproduction
- **Testes** of short-day hamsters smaller than long-day hamsters
- Melatonin was used at high doses for birth control by women in Holland
Glutamate

- excitatory - inputs to hippocampus -
- maybe half of CNS synapses
- Synthesis is simple from glutamine (from nearby glia) by glutaminase.
- Affected by many toxins, for instance poison from mussels - domoic acid, and plants (Box).
- Involvement in ALS (Amyotrophic lateral sclerosis [Lou Gehrig's] ALS) and possibly Alzheimers.
more

- Excitotoxicity - Box 6C
- too much glutamate causes a cycle of Ca2+ influx.
- May be involved in ischemia - induced injury.
GABA

• (gamma amino butyric acid) inhibitory
• synthesis GAD glutamic acid decarboxylase made in a shunt in the TCA (Kreb's) cycle, present in brain
• There is a lot of GABA in the brain, mostly local circuits, but also Purkinje output.
• Incidentally, a natural breakdown product of GABA is gamma hydroxy butyrate (GHB), the date rape drug.
Glycine

- Glycine is the other major inhibitory transmitter
- transporter mutation causes hyperglycenemia - neonatal seizures, lethargy, retardation
- synthesis by serine hydroxymethyltransferase
- a lot in the spinal cord
- strychnine blocks
(A) Histidine

\[
\text{Histidine} \xrightarrow{\text{Histidine decarboxylase}} \text{CO}_2
\]

Histamine

(B) Tryptophan

\[
\text{Tryptophan} \xrightarrow{\text{O}_2} \text{Tryptophan-5-hydroxylase} \rightarrow 5\text{-Hydroxytryptophan} \xrightarrow{\text{Aromatic L-amino acid decarboxylase}} \text{CO}_2
\]

Serotonin (5-HT)
Chemical neuroanatomy

• 1960's histochemical fluorescence
  Expose sections to paraformaldehyde
• neurotransmitters widespread effects
• but come from defined locations
• Dopamine from substantia nigra
• Norepinephrine from locus coeruleus
• Serotonin from Raphe
Parkinson’s

- degeneration of substantia nigra
- 1817 Shaky palsey
- Degenerate dopaminergic input to striatum
- Cells that survive - inclusions Lewy bodies
- bradykinesia, akinesia, rigity, stilted gait, tremors, walk in shuffle, stone (expressionless) face, loss of affect.
- 1% of people over 50 years old
more

- Lateral hypothalamic lesions make thin rat motivational defects, dopamine in medial forebrain bundle toward basal ganglia.
- Dopaminergic neurons degenerate,
- animal model - 6-OHDA uptake makes peroxide, cells die.
- Cannot give dopamine not cross the blood brain barrier.
Parkinson’s continued

• Give L-DOPA (in large doses because L-AADeCOOHase is everywhere);
• give decarboxylase inhibitor carbidopa.
• Extrapyramidal motor syndrome also comes from long term administration of antipsychotic phenothiazines such as chlorpromazine (brand name Thorazine).
• (Chronic use of these drugs also cause a corioretinopathy.)
Parkinson’s (4)

- bad batch of street drugs with MPTP.
- rotenone, and others, are like MPTP.
- cell transplant therapies - controversial.
- Carlsson shared 2000 Nobel Prize
- the late Pope, Mohammad Ali, Michael J Fox.
- Mostly it is "sporadic" (not genetic)
- familial cases have been interesting.
- Alpha-synuclein, Parkin and DJ-1.
Psychiatry

- Psychosis vs Neuroses
- Schizophrenia (dementia praecox= early loss of intelligence) (paranoid, catatonic, etc.),
- thought disorders, progressive, degenerative
- more "hospitalization" than everything else
- "insane asylums" (These were the days before political correctness.)
- Borris Karloff old movie "Bedlam" is about insane asylum.
Psychiatry

• Mistrust, personal reflection, "One flew over the cuckoo's nest" with Jack Nicholson (1975)
• Alumnus interview: prozac-suicide, treating teens, dexedrene to treat hyperactivity, Tom Cruise-ritalin, Brooke Shields post partum depression, shock therapy, drug specificity
Changing treatments

• Reserpine storage blocker, used for hypertension (for NE [and DA, 5HT])
• (nowadays, the disparaging phrase is "went off his or her meds").
• 1960s ad "mental illness [again before pc] is no longer hopeless"
• (that kids used to say to each other).
• D.W. Woolley, The biochemical bases of psychoses (subtitle - the serotonin hypothesis about mental diseases) LSD serotoninergic
Changing transmitters

- band wagons
- norepinephrine theory of affective disorders
  Stein also Schildkraut and Kety
- amphetamine causes psychosis
- Amphetamine stimulates NE release
- Methedrine, dexedrine (diet pill and ADHD), benzedrine, ritalin used for ADHD
- odd - stimulants for hyperactivity;
- controversial that kids are given such drugs.
  amphetamine cocaine regulated transcription factor.
Dopamine over-activation

- Dopamine receptor blockers (antagonist) - haloperidol, chlorpromazine are antipsychotics.
- Chronic chlorpromazine treatment causes chorioretinopathy and Parkinson's tremors.
- Incidentally, a controversial 1971 book (D. Rosenthal, Genetics of psychopathology) suggested an underlying genetic predisposition for schizophrenia, now widely believed.
Depression

- unipolar, bipolar (manic depression) involutional melancholy (in elderly)
- Bipolar seems to run in families,
- treated with lithium salt
- Li+ can replace Na+ for the action potential but not in the Na+ pump, action potentials would be smaller.
- Unipolar Tricyclic antidepressants (desipramine) blocks NE (and other) reuptake.
- SSRI's covered above.
Treating depression

- Antidepressants MAOI's (phenylzine)
- After electroconvulsive shock (ECS), patients seem much happier;
- sounds barbaric, but still used and, with correct control medications, it is not cruel;
- memory loss for the time before the shock,
- ECS fits in with the idea that correctly reverberating neural circuits are important for memory consolidation.
Treating other disorders

• Anxiety - Tranquillizers - benzodiazepines (chlordiazepoxide = Librium, diazepam = Valium) enhance GABA-A receptors

• Treat panic with MAOI's, also serotonin receptor blockers, also benzodiazepine alprazolam (Xanax).
Peptides

- Substance P - 11 amino acids known for 60 years, named after "powder" involved in pain
- Pert & Snyder, Opiate receptor: 1973,
- Tritiated naloxone, opiate antagonist, binds to places in the brain and is displaced by opiates in parallel with their strength.
- While you have receptors but do not know what the ligand is [yet], these are called "orphan receptors."
Peptide ligands

• endogenous opiates (enkephalins, endorphins dynorphins)
• met-enkephalin and leu-enkephalin, 5 amino acids
• beta-endorphin 31 amino acids
• cleaved from pro-opiomelanocortin or proenkephalin precursor
<table>
<thead>
<tr>
<th>Name</th>
<th>Amino acid sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endorphins</strong></td>
<td></td>
</tr>
<tr>
<td>α-Endorphin</td>
<td>Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr</td>
</tr>
<tr>
<td>α-Neoendorphin</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys</td>
</tr>
<tr>
<td>β-Endorphin</td>
<td>Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr- Leu-Phe-Lys-Asn-Ala-Ile-Val-Lys-Asn-Ala-His-Lys-Gly-Gln</td>
</tr>
<tr>
<td>γ-Endorphin</td>
<td>Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu</td>
</tr>
<tr>
<td><strong>Enkephalins</strong></td>
<td></td>
</tr>
<tr>
<td>Leu-enkephalin</td>
<td>Tyr-Gly-Gly-Phe-Leu</td>
</tr>
<tr>
<td>Met-enkephalin</td>
<td>Tyr-Gly-Gly-Phe-Met</td>
</tr>
<tr>
<td><strong>Dynorphins</strong></td>
<td></td>
</tr>
<tr>
<td>Dynorphin B</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr</td>
</tr>
</tbody>
</table>

*Note the initial homology, indicated by italics.*
From outline

- Cannabis sativa Scientific American,
- anxiety, pain, nausea, obesity, glaucoma.
- hypothalamus, basal ganglia, amygdala, brain stem, cortex, hippocampus, cerebellum.
- Howlett, 1988, SLU, receptor CB1, later CB2
- G protein coupled receptors.
- Presynaptic CB1 prevents GABA release to block glutamate excitation
(A) Alkyl Acyl Phosphatidylethanolamine

\[ \text{N-Acyltransferase} \]

N-Acylphosphatidylethanolamine

\[ \text{N-Arachidonoyl phosphatidylethanolamine} \]

\[ \text{Phospholipase D} \]

Anandamide