Lecture 6

-Acetylcholine
  -Synthesis:

  CoA (mitochondria) → Acetyl-CoA → Ach (destroyed by AchE)
  Acetate (vinegar, food) → Choline (lipids, food) → CoA

-Found:
  -Pons (REM sleep)
  -Basal forebrain (learning in cortex, long term memory)
  -Medial septum (brain rhythms, short term memory in hippocampus)
  -Peripheral nervous system (muscle contraction)

-Receptors: Mostly excitatory
  -Nicotinic: ionotropic (Na+), stimulated by nicotine
  -Muscarinic: metabotropic

-Psychopharmacology
  -First neurotransmitter discovered
  -ACh is involved in muscle contractions
  -Parasympathetic system: digestion, sexual arousal, decrease in heart rate
  -Botulinum toxin blocks ACh release (paralysis, death, wrinkles), produced by bacteria, poisonous, naturally occurring substance, used medically
  -Black widow spider promotes ACh release (agonist), convulsion, death.
  -Neostigmine (AChE inhibitor, does not cross BBB, PNS only), agonist. Reduces myasthenia gravis symptoms.
  -Atropine blocks muscarinic receptors (antagonist) response to nerve gas
  -Curare blocks nicotinic receptors (paralysis, surgical procedures to prevent muscle contractions)

-Mono amine: Catecholamines: Dopamine
  -Synthesis:

  Tyrosine (high protein foods) → L-Dopa → Dopamine

-Found: Midbrain
  -Substantia nigra: projects to basal ganglia (movement): nigro striatal
  -Ventral tegmental area: projects to limbic cortex (reinforcement, desire, emotions), Mesolimbic
  -projects to prefrontal cortex (planning, problem solving, Mesocortical)

-Receptors: Excitatory or inhibitory
  D1, D2, D3, D4, D5
Psychopharmacology
- Pleasure system: positive reinforcement, drug addiction
- Parkinson's disease (low levels of DA)
  - damage of connections: subnigra → caudate
  - dopamine doesn't cross BBB. (L-Dopa does)
- deep brain stimulation (prevent tumors)
- Schizophrenia (high levels of DA)
  - Chlorpromazine blocks dopamine D2/4 receptors
  - AMPT blocks enzyme (tyrosine -> L-Dopa)
  - Reserpine prevents storage of monoamines in vessels
  - Amphetamines and cocaine = DA reuptake inhibitors. Addiction.
    - Methamphetamines: crystal meth (also affects levels of NE)
    - Methylphenidate: (Ritalin), treats ADD
- Monoamine oxidase destroys (oxidizes) excessive monoamines. Found naturally in blood.
  - (Cheese, chocolate control) - too much MAO is linked with depression. Deprenyl destroys MAO and increases vesicle content of DA.
- MAO inactivates free floating dopamine molecules

Mono amine: Nor/epinephrine (NE/E) aka adrenalin
- Synthesis: tyrosine → L Dopa → dopamine → norepinephrine
- Found:
  - Norepinephrine: locus coeruleus (dorsal pons)
  - Epinephrine: (hormone) produced in adrenal medulla.
- wide projections throughout brain
- Release at axonal varicosities (diffuse release)
- Receptors: Excitatory or inhibitory
- Psychopharmacology:
  - Vigilance and attention
  - Fusaric acid blocks synthesis of NE from dopamine
  - Reserpine prevents storage of monoamines in vesicles.
- Idazoxan blocks autoreceptors (stops regulation of release)
- Norepinephrine: localized production, diffuse projections.

Mono amine: Serotonin (5-HT)
- Synthesis: tryptophan -> 5-HT -> 5-hydroxytryptamine
- Found:
  - Mainly: Raphe nuclei (midbrain)
  - Released at axonal varicosities (diffuse release)
- Receptors: Excitatory or inhibitory. 9 kinds
- Psychopharmacology:
  - Mood, eating, vomiting. Sleep (dreaming), pain
  - PCPA blocks tryptophan -> 5-HTP reaction
  - Fluoxetine (Prozac) inhibits 5-HT reuptake
  - Fenfluramine inhibits 5-HT reuptake, stimulate release, appetite suppressing
  - LSD (acid) is hallucinogenic. Multiple sites of action on 5-HT. Agonist for 5-HT2A
Serotonin: localized production, diffuse projections.
Neuro peptides:
- Synthesis:
  - In soma, from many amino acids. Need axoplasmic transport
  - 100 kinds
  - Transmitters: endogenous opioids (enkephalins, endorphins)
- Found:
  - Many regions of CNS and PNS
  - Released at synaptic boutons, and by volume transmission
  - Co-released with other neurotransmitters (same vesicles)
  - Deactivated by enzymes
- Receptors: usually inhibitory
  - Many!
  - For enkephalins: δ-receptor, μ-receptor, and κ-receptor
  - For opioid peptides: opiate receptors
- Psychopharmacology:
  - Opium, morphine, heroine (opiates): bind to/open opiate receptors
  - Codeine: cough suppressant. Converted in liver to morphine
  - Naloxone: blocks opiate receptors (prevents overdose)
  - Angiotensin: PNS constrict blood vessels. CNS: thirst

Lipids:
- Synthesis: Anandamide (endo-cannabinoids)
- Found: (non local). Produced on demand, not stored in vesicles.
- Receptors: Excitatory or inhibitory
  - Many metabotropic: CB1, CB2
- Psychopharmacology:
  - Complex synaptic effects. THC is agonist
  - THC (marijuana): Analgesic, sedative, appetite enhancer.
  - Chemotherapy. Blocks 5-HT3 (anti-vomiting)
  - THC interferes with attention, distort perception (time and space). Impairs learning and memory. May be addictive at high doses.
  - Synthetic THC prescribed for chemo and multiple sclerosis
  - Acetaminophen (Tylenol): acts on CB1 receptors (agonist)
  - Rimonabant: blocks CB1 receptors (antagonist)

Nucleosides:
- Synthesis: sugar molecule bound to other compounds (adenosine)
- Found: Non local, adenosine: released by astrocytes
- Receptors: Many! For adenosine, 3 types of receptors. Inhibitory through a metabotropic K+ channel. Triggered by low energy and low oxygen signals.
- Psychopharmacology:
  - Physiological: increase in blood flow
  - Neural: decrease in arousal (involved in sleep)
  - Caffeine is an adenosine receptor blocker. Addictive (withdrawal), crosses placenta
  - Caffeine passes through BBB, is a fat-soluble. Passes through cell membranes.
Soluble gases

- Synthesis:
  - Nitric oxide (NO) within neurons, no storage
  - Carbon monoxide (CO)
- Found: Non local
- Receptors:
  - None. Diffuse directly into neighboring neurons
  - Triggers second messenger cascades
- Psychopharmacology:
  - Modulates intestine function (relaxation)
  - Stimulate erection (vasodilator). Viagra is NO inhibitor blocker
  - Involved in learning and memory