Receptors and Neurotransmitters Continued

Psychology 472: Pharmacology of Psychoactive Drugs

Neurotransmitter Classes
- Acetylcholine (ACh)
- Catecholamines
  - Dopamine (DA)
  - Norepinephrine (NE)
- Serotonin (5-HT)
- Amino Acids
  - Glutamate = Excitatory
  - GABA = Inhibitory
- Peptide Neurotransmitters
  - e.g., Endorphins, Enkephalins

Functions
- Role in awakening systems in the brain
- Has a role in memory
- Decrease of ACh neurons is correlated with Alzheimer's and other diseases

Acetylcholine
- Acetylcholine (ACh) is the primary NT secreted by efferent CNS cells
- In the periphery: ACh neurons are found in:
  - Autonomic ganglia (e.g., the heart)
  - The neuromuscular junction (activation of muscle movement)
- In Brain: ACh neurons are found in:
  - Dorsolateral pons
  - Medial septum
  - Basal forebrain
  - ACh release in brain results in facilitatory effects

ACh Pathways
- Septal nucleus and nucleus basalis
  - Projects to forebrain.
- Midbrain
  - Projects to reticular formation, pons, cerebellum, and cranial nerve nuclei.
Cholinergic System

Acetyl-CoA
(in mitochondria, involved in Krebs cycle) + Choline (from diet)

ACh Receptors
- Two Types
- Nicotinic receptors are found in skeletal muscle (ionotropic effect)
  - Agonists: ACh, nicotine
  - Antagonists: d-tubocurarine and curare
- Muscarinic receptors are found in heart and smooth muscle (metabotropic effects)
  - Agonists: ACh, muscarine
  - Antagonists: Atropine and scopolamine

Nicotinic Receptor
- Receptor and ion channel are one unit
- ACh binds to alpha subunit
- Beta and Delta subunits are concerned with regulatory functioning

Muscarinic Receptors
- Uses a GP second messenger system
  - Ach
  - Muscarinic Ach Receptor
  - Gp
  - PLC
  - IP-3
  - DAG
  - Ca Release
  - PKC

If you put a phosphate group on Beta or Delta subunits – causes endocytosis. Receptor enters post synaptic element and is destroyed – Decreases sensitivity
AChE Inhibitors
- Irreversible
  - Often toxic
  - Include pesticides and nerves gases
- Reversible
  - Cognitive enhancers
  - Treating Alzheimer's

Amino Acid Transmitters
- Synthesis
  - Glutamine
    - Glutaminase
      - Glutamate = Excitatory
      - GABA = Inhibitory (more than half the synapses in the brain)

GABA
- Is synthesized from glutamic acid
- Induces IPSPs
- Acts via 2 receptors
  - \( \text{GABA}_A \): Ionotropic receptor (controls a chloride channel)
  - \( \text{GABA}_A \) receptors contain 5 distinct binding sites
    - GABA site
    - Benzo diazepine site
    - Barbiturates
    - Steroid binding site
    - Picrotoxin binding site

Gaba Cycle
- Metabolized by GABA-transaminase (GABA-T)
- Termination
  - reuptake with transporters on neuron or glial cells
GABA
- Activates a metabotropic receptor (controls a K⁺ channel)
- Formed by subunits (GABA-B1 [has 2 forms] and GABA-B2).

Amino Acids
- Drugs
  - Glutamate
    - PCP/ketamine (antagonists)
    - GABA
      - Sedative-hypnotics – tranquilizers, alcohol...
  - (agonists)

Glutamate
- Comes from metabolic pathway (Krebs cycle) or from glutamine via glutaminase.
- Binds to several receptor types.
  - NMDA, kainate, AMPA
    - NMDA mediated by glutamate and glycine-serine.
    - NMDA requires membrane depolarization by kainate or AMPA.
    - NMDA involved in memory formation.

Disorders
- Glutamate
  - Epilepsy / seizure
  - Dementias?
- GABA
  - Epilepsy / seizure
Biogenic Amine Transmitters

Catecholamine Synthesis

Dopamine
- Is used by several neural systems
  - Nigrostriatal system
    - Projects from the substantia nigra to the caudate nucleus and putamen
  - Mesolimbic system
    - Projects from ventral tegmental area to the limbic system (including the nucleus accumbens, amygdala, and hippocampus)
  - Mesocortical system projects from the ventral tegmental area to the cortex

Dopamine receptors are metabotropic
- D1 receptors are postsynaptic, whereas D2 receptors are pre- and postsynaptic
Receptors

- Dopamine
  - Two families: D1 and D2
  - DA and NE do not directly activate ion channels, but trigger sequence of chemical events.

Dopamine Pathways

Norepinephrine

- Norepinephrine is synthesized from dopamine within vesicles
- The locus coeruleus gives rise to NE fiber systems
  - NE is secreted from varicosities along fibers
  - NE interacts with four receptor types in brain
    - $\alpha$-adrenergic (subtypes 1 and 2)
    - $\beta$-adrenergic (subtypes 1 and 2)
    - Adrenergic receptors are metabotropic

Serotonin Synthesis

PCPA inhibits TH
Serotonin
- Synthesis
  - Tryptophan
- Receptors
  - Ionotropic
    - 5-HT₃
  - G protein-coupled
    - 5-HT₁A, 5-HT₂, 5-HT₄
- Pathways
  - Largely parallel
  - DA

(5-HT) cells are mostly located in the gut (98%) with only 2% of serotonin cells in brain
- Serotonin cell bodies are located in brainstem raphe nuclei and project to cortex
- Serotonin systems:
  - D system originates in the dorsal raphe nucleus but does not form synapses (5-HT as a neuromodulator)
  - M system originates from the median raphe nucleus and these varicosities form synapses

Serotonin: Release and Termination
- Serotonin release:
  - 8-OHDPAT is an autoreceptor agonist that reduces 5-HT release
  - No selective release blocker
  - Fenfluramine is a 5-HT releasing drug
- Serotonin termination:
  - Reuptake is blocked by fluoxetine (elevates 5-HT)
  - Degradation: MAO converts serotonin to 5-HIAA

Glutamate
- Glutamate (glutamic acid) is an excitatory neurotransmitter
- Glutamate interacts with four receptor types
  - NMDA receptor: controls a CA²⁺ channel
    - Activation by glutamine requires glycine binding and displacement of magnesium ions
  - AMPA receptor: controls sodium channels
  - Kainate receptor: controls sodium channels
  - Metabotropic glutamate receptor
Peptides

- Consist of 2 or more amino acids
- Are synthesized in the soma and transported to the presynaptic element in vesicles
- Are released from all parts of the presynaptic element
- After release are enzymatically degraded (no reuptake)
- Peptides can be co-released with other NTs
  - Serves as neuromodulators

Peptides

- More than 100 types
- Are small proteins
  - Have 30 - 40 amino acids
- Are critical for fine tuning the NS

Conclusions

- Lots of different types
- Lots of different functions
- Impact multiple brain systems
- Important to have a general idea about what they do and the systems they impact