Carlson (7e)

PowerPoint Lecture Outline

Chapter 4: Psychopharmacology

Psychopharmacology

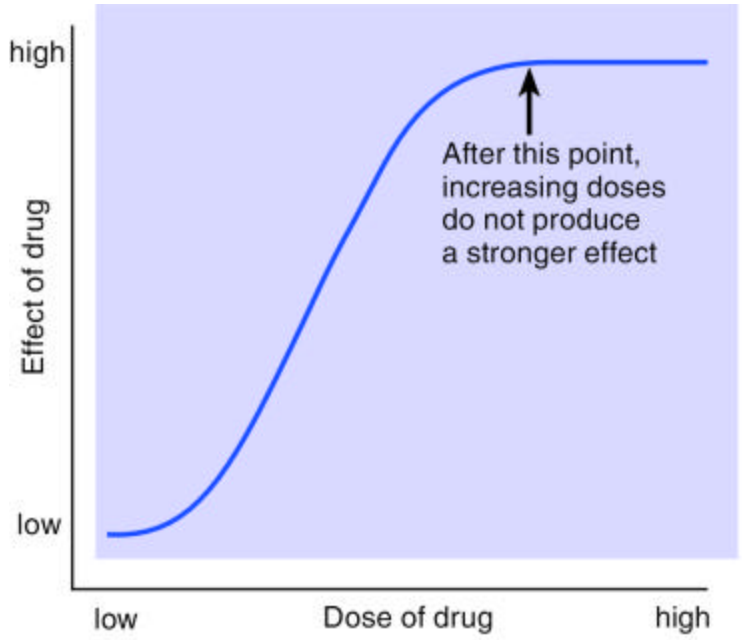
- Psychopharmacology is the study of the effects of drugs on the nervous system and on behavior
- The term drug has many meanings:
  - Medication to treat a disease
  - A chemical that is likely to be abused
  - An "exogenous" chemical that significantly alters the function of certain bodily cells when taken in relatively low doses (chemical is not required for normal cellular functioning)

Pharmacokinetics

- Drug molecules interact with target sites to effect the nervous system
  - The drug must be absorbed into the bloodstream and then carried to the target site(s)
- Pharmacokinetics is the study of drug absorption, distribution within body, and drug elimination
  - Absorption depends on the route of administration
  - Drug distribution depends on how soluble the drug molecule is in fat (to pass through membranes) and on the extent to which the drug binds to blood proteins (albumin)
  - Drug elimination is accomplished by excretion into urine and/or by inactivation by enzymes in the liver

Drug Effectiveness

- Dose-response (DR) curve: Depicts the relation between drug dose and magnitude of drug effect
- Drugs can have more than one effect
- Drugs vary in effectiveness
  - Different sites of action
  - Different affinities for receptors
- The effectiveness of a drug is considered relative to its safety (therapeutic index)



Routes of Drug Administration

- Routes of drug administration into the body
  - Intravenous (IV): into a vein (rapid absorption)
  - Intraperitoneal (IP): into the gut (used in lab animals)
  - Subcutaneous (SC): under the skin
  - Intramuscular (IM): into a muscle
  - Inhalation of the drug into the lungs
  - Topical: absorbed through the skin
  - Oral (PO): via the mouth

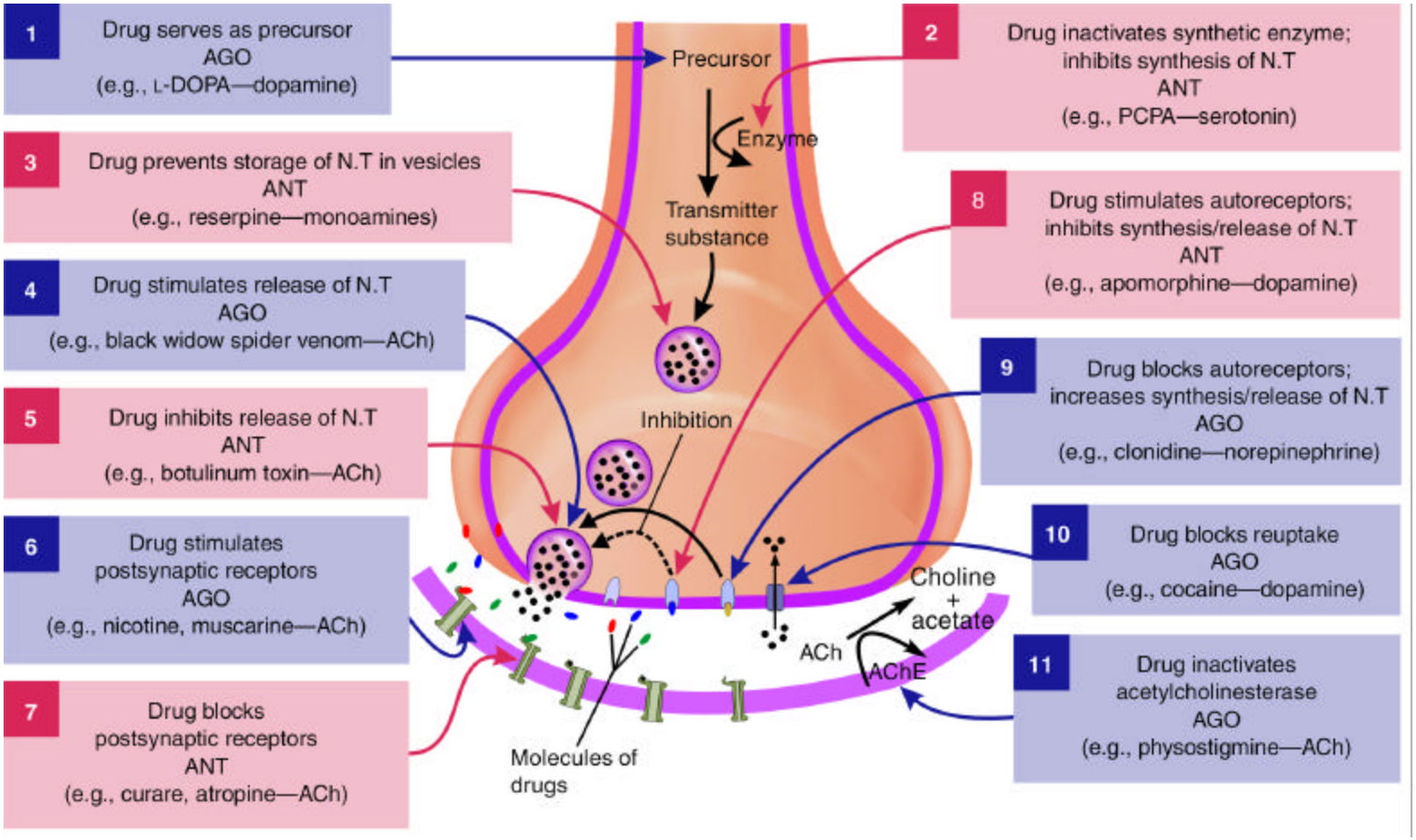
Tolerance and Sensitization

- Repeated administration of a drug can alter its subsequent effectiveness
  - Tolerance: Repeated drug administration results in diminished drug effect (or requires increased dosage to maintain constant effect)
    - Withdrawal effects are often the opposite of the drug effect and often accompanies tolerance
    - Tolerance can reflect decreased drug-receptor binding or reduced postsynaptic action of the drug
  - Sensitization: Repeated drug administration results in heightened drug effectiveness

Synaptic Transmission

- Transmitter substances are
  - Synthesized, stored, released, and terminated
  - Susceptible to drug manipulation
- Definitions:
  - Direct agonist: a drug that binds to and activates a receptor
  - Antagonist: a drug that binds to but does not activate a receptor
    - Indirect antagonists are drugs that attach to a binding site and interfere with the normal action of the receptor

Drug Action on Synaptic Transmission



Agonist drugs are in red, Antagonists are in blue

Presynaptic Drug Actions

- Presynaptic autoreceptors regulate the amount of NT released from the axon terminal
  - Drugs that activate presynaptic autoreceptors reduce the amount of NT released, an antagonistic action
  - Drugs that inactivate presynaptic autoreceptors increase the amount of NT released, an agonistic action
- Presynaptic heteroreceptors are sensitive to NT released by another neuron, can be inhibitory or facilitatory

Neuromodulators

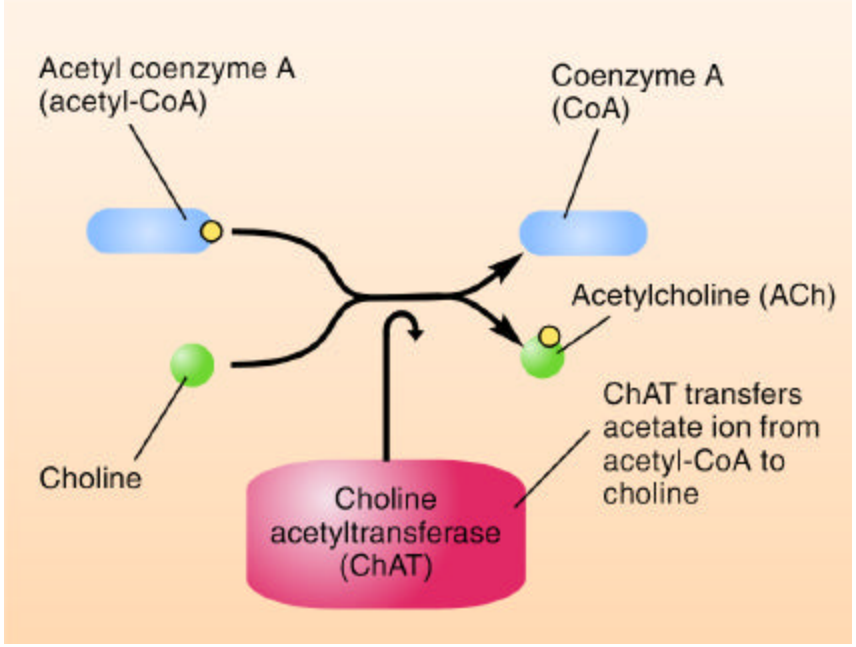
- Neurotransmitter binding to receptors produces either EPSPs or IPSPs
  - Glutamate produces EPSPs
  - GABA produces IPSPs
- Neuromodulators alter the action of systems of neurons that transmit information using either glutamate or GABA

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

Synthesis of ACh

- ACh synthesis pathway:
  - Acetyl CoA+Choline → ACh
  - CoA arises from glucose metabolism
  - Synthesis is dependent on choline
  - ACh synthesis is blocked by NVP



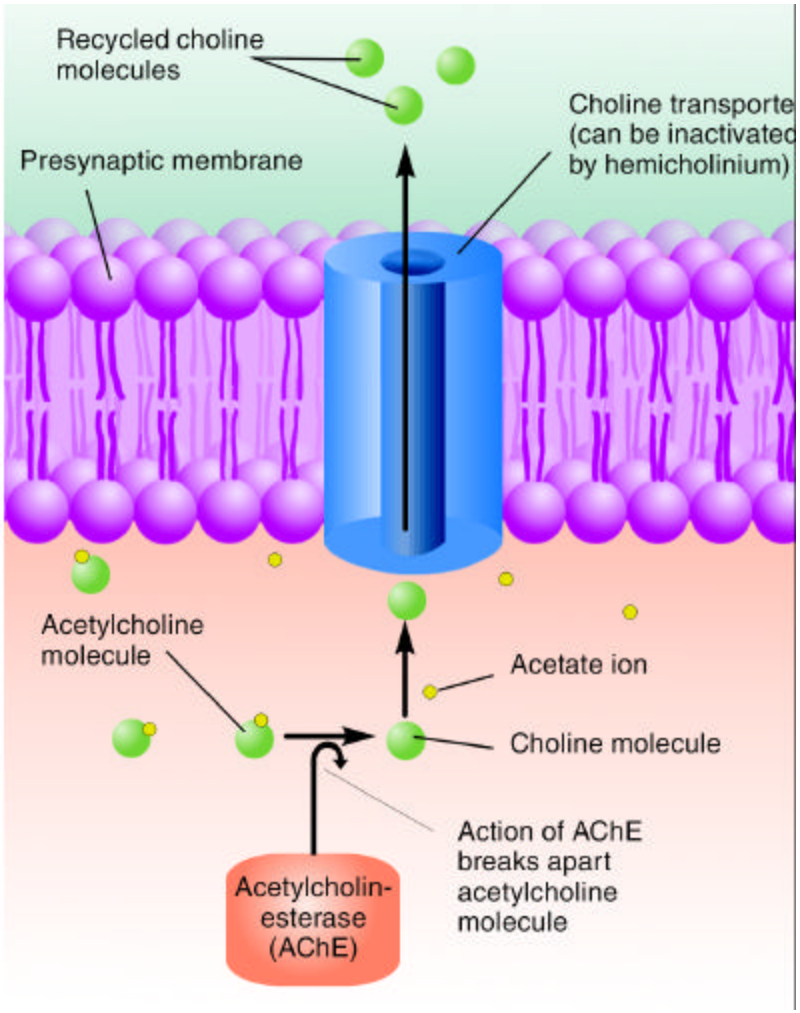
Drug-ACh Interactions

- Choline is required for ACh synthesis
  - Hemicholium inhibits the reuptake of choline
- ACh release
  - Requires calcium ion entry
  - ACh release is blocked by botulinum toxin
  - ACh release is promoted by black widow spider venom
- ACh is degraded by AChE
  - Neostygmine interferes with AChE activity

ACh Receptors

- Nictotinic 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

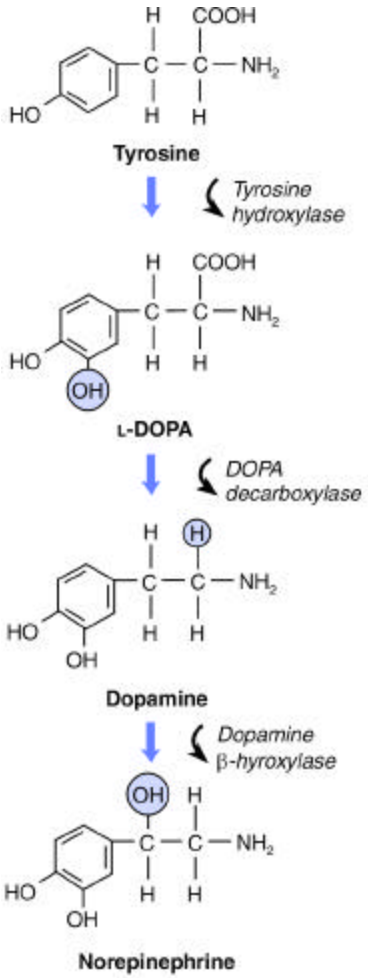
Termination of ACh Effect



Monoamine Neurotransmitters

- The monoamine transmitters share a common structure and form a family of neurotransmitters
  - Catecholamines include dopamine (DA), norepinephrine (NE), and epinephrine (EPI)
  - Indolamines include serotonin (5-HT)
- The cell bodies of monoamine neurons are located in the brainstem and give rise to axon terminals that are distributed widely throughout the brain

Catecholamine Synthesis



Dopamine

- 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

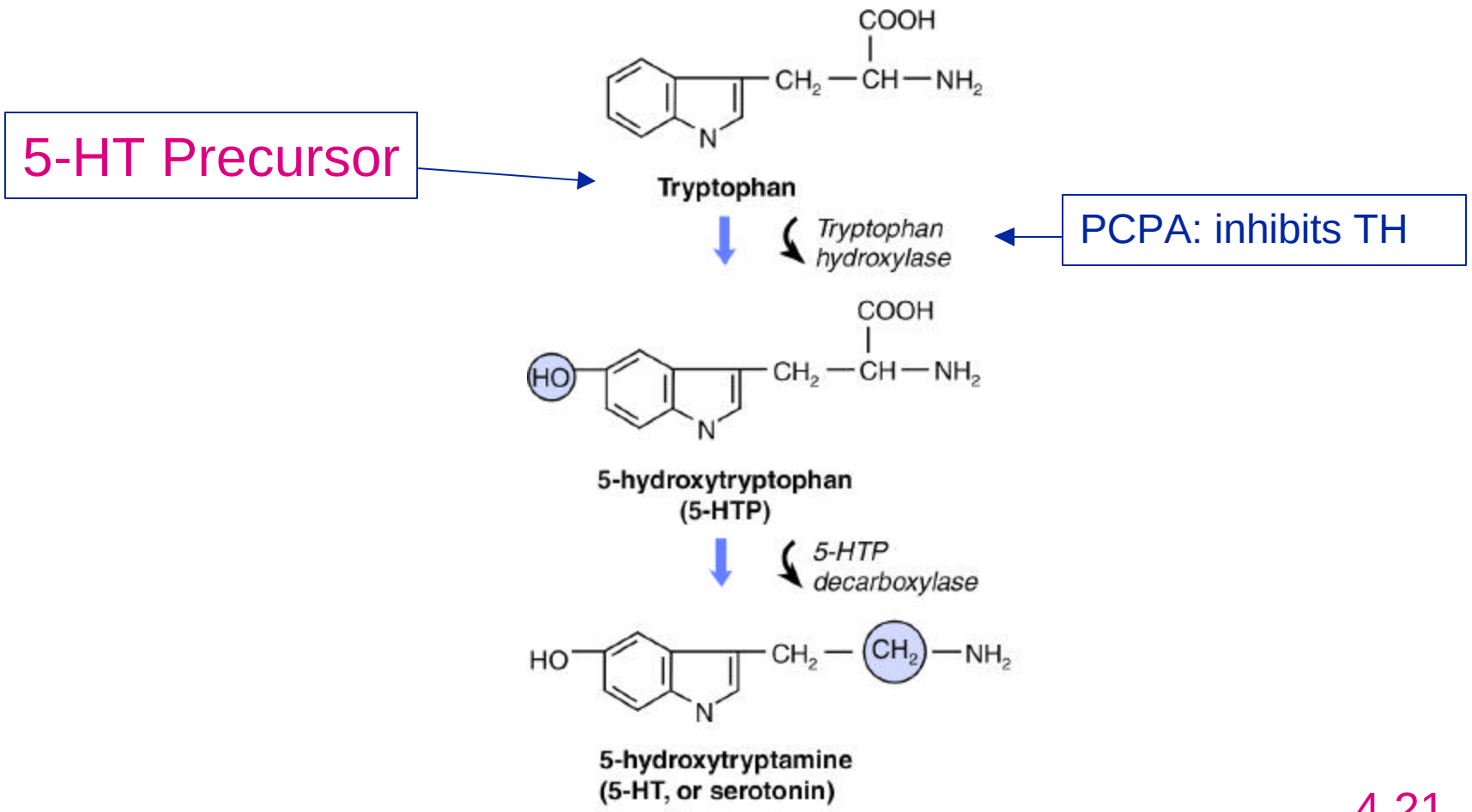
Drug-Dopamine Interactions

- AMPT blocks tyrosine hydroxylase, preventing the conversion of tyrosine to l-DOPA
- Reserpine prevents the storage of dopamine within vesicles
- Cocaine blocks the reuptake of dopamine
- Monoamine oxidase (MAO) within the axon terminal degrades dopamine
  - Deprenyl blocks MAO-B to increase dopamine

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
  - α-adrenergic (subtypes 1 and 2)
  - β-adrenergic (subtypes 1 and 2)
  - Adrenergic receptors are metabotropic

Serotonin Synthesis



Serotonin

- Serotonin (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

5-HT: 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 5HT)
  - Degradation: MAO converts serotonin to 5-HIAA

Serotonin Receptors

- There are at least 9 types of 5-HT receptors
  - 5-HT_1 : 1A, 1B, 1D, 1E, and 1F
  - 5-HT_2 : 2A, 2B, and 2C
  - 5-HT_3
- 5-HT_3 receptors are ionotropic, the remainder are metabotropic
- 5-HT_{1B} and 5-HT_{1D} are presynaptic autoreceptors

Glutamate

- Glutamate (glutamic acid) is an excitatory neurotransmitter
- Glutamate interacts with four receptor types
  - NMDA receptor: controls a CA^{++} 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

GABA

- GABA is synthesized from glutamic acid
- GABA induces IPSPs
- GABA acts via 2 receptors
  - $GABA_A$: ionotropic receptor (controls a chloride channel)
  - $GABA_A$ receptors contain 5 distinct binding sites
    - GABA site
    - Benzodiazepine site
    - Barbiturates
    - Steroid binding site
    - Picrotoxin binding site
  - $GABA_B$: metabotropic receptor (controls a K^+ channel)

Peptides

- Peptides consist of 2 or more amino acids (linked by peptide bonds)
- Peptides are synthesized in the soma and transported to axon terminal in vesicles
- Peptides are released from all parts of the terminal button and after release are enzymatically degraded (no reuptake)
- Peptides can be co-released with other NTs
  - Peptide can serve as neuromodulator

Lipids

- THC interacts with cannabinoid (CB) receptors in brain to produce analgesia and sedation
- There are two endogenous ligands for the CB receptors, each is derived from lipid precursors
  - Anandamide
  - 2-arachidonyl glycerol (2-AG)
- Anandamide interferes with 5-HT_3 receptors to reduce vomiting and nausea

Soluble Gases

- Soluble gases can diffuse widely to exert actions on distant cells
- Nitric oxide (NO) is created within cells from the amino acid arginine
  - NO exerts effects within intestinal muscles, dilates brain blood vessels, and contributes to the changes in blood vessels that produce penile erections
  - NO activates an enzyme that produces cyclic GMP (a second messenger) within adjoining cells