CNS NEUROTRANSMITTERS

(1) **Amino acids** (primarily glutamic acid, GABA, aspartic acid & glycine)

(2) **Peptides** (vasopressin, somatostatin, neurotensin, enkephalines, etc.

(3) **Biogenic amines** (e.g. Monoamines: norepinephrine, dopamine & serotonin, and acetylcholine).
I. Some (like glutamate) are excitatory, whereas others (like GABA) are primarily inhibitory.

II. In many cases (as with dopamine) it is the receptor which determines whether the transmitter is excitatory or inhibitory.
GLYCINE

- The simplest amino acid, consisting of an amino group and a carboxyl (acidic) group attached to a carbon atom.
- When released, glycine binds to a receptor resulting in opening of Cl⁻ ion channel. This hyperpolarizes the postsynaptic membrane.
  Thus, glycine is an inhibitory transmitter.
- It is inactivated by active transport (reuptake) back into the presynaptic membrane.
I. The glycine receptor is primarily found in the ventral spinal cord.

II. The poison Strychnine is a glycine antagonist which can bind to the glycine receptor (i.e., it inhibits inhibition). This results in spinal hyperexcitability (causes convulsions).

III. Strychnine causes violent tetanic convulsions in which the body is arched and the head bent backward. After a minute the muscles relax. A touch, a noise or some other stimulus causes the convulsions to recur;
Aspartate

- Apartate is released in the spinal cord. It is an excitatory neurotransmitter, which increases the likelihood of depolarization in the postsynaptic membrane.
- Aspartate & glycine form an excitatory/inhibitory pair in the ventral spinal cord.
- Glutamate & GABA form an excitatory/inhibitory pair in the brain.
Glutamate

- Glutamate is the most common neurotransmitter in the brain. It is always excitatory.

- Glutamate receptors are:
  - ionotrophic (ion channel coupled) receptors:
    - NMDA receptor
    - AMPA receptor (aminomethyl propionic acid)
    - Kainate receptor
  - Metabotropic receptors (G-protein coupled)
• The most important Glutamate receptor is the NMDA glutamate receptor. (N-Methyl-D-Aspartate is a synthetic chemical not naturally found in biological systems, but it binds specifically to the NMDA glutamate receptor)
The NMDA receptor is the only known receptor which is regulated both by a ligand (glutamate) and by voltage.

There are at least 5 binding sites which regulate NMDA receptor activity, 
*These* sites are for (1) glutamate (2) glycine (3) magnesium (4) zinc and (5) a site that binds the hallucinogenic substance phencyclidine (PCP, "angel dust").

N.B. Phencyclidine can induce psychosis
I. NMDA receptors are most densely concentrated in the cerebral cortex, hippocampus, amygdala, & basal ganglia.

II. They are particularly vulnerable to glutamic acid excitotoxicity, *i.e.*, damaging effects due to excessive excitatory neurotransmitter release. Both aspartic acid & glutamic acid (the two amino acids having 2 carboxyl groups -- the "acidic amino acids") have the capacity for destroying neurons when released in excessive amounts
I. Glutamate released into synapses is either reabsorbed directly into neurons, or is soaked-up by astrocytes (glial cells) which convert the glutamate into glutamine (a molecule which cannot cause excitotoxicity). The glutamine can then be safely transported back to neurons for re-conversion into glutamate.

II. Excitotoxicity due to glutamic acid is a major destructive process seen in strokes and other forms of brain ischemia
Glutamate antagonists

• May be useful in:
  • Treatment of epilepsy
  • Treatment of schizophrenia
  • Brain cell death caused by excessive glutamic acid release
I. GABA is the major inhibitory neurotransmitter of the brain.

II. It is most highly concentrated in the substantia nigra & globus pallidus nuclei of the basal ganglia.

III. Like glycine, the GABAA receptor is connected to a chloride ion channel. This hyperpolarizes the postsynaptic membrane. GABAB receptor is a G-protein coupled receptor.
Acetylcholine

I. Acetylcholine is usually (but not always) an excitatory neurotransmitter -- in contrast to the monoamine neurotransmitters, which are nearly always (with a few exceptions) inhibitory.

II. Centrally-acting muscarinic blocking agents result in memory loss for normal individuals. In Alzheimer's Disease patients, cholinergic loss could be an important factor in memory loss for these patients.
Monoamines

- The primary monoamines are:
  - dopamine,
  - norepinephrine
  - serotonin.

Dopamine and norepinephrine are catecholeamines, whereas serotonin is an indolamine.
Dopamine

Dopamine receptor-types
There are two primary dopamine receptor-types, both of which act through G-proteins:

- $D_1$ (stimulatory)
- $D_2$ (inhibitory),

$D_2$ receptors often occur on the dopaminergic neurons. They are called autoreceptors and upon stimulation can inhibit both dopamine synthesis and release.
I. Depletion of striatal dopamine to 20% the original level, symptoms of Parkinson's Disease appear. L-DOPA is the treatment.

II. Schizophrenia is thought to be due to an overstimulation of $D_2$ receptors in the mesolimbic and mesocortical systems. 

$D_2$ antagonist drugs alleviate the symptoms, whereas substances which increase $D_2$ stimulation, such as amphetamines, can induce psychotic symptoms resembling schizophrenia.
Other actions of dopamine:
- Induction of vomiting by stimulation of \( D_2 \) cells in the chemoreceptor trigger zone,
- Stimulation of growth hormone release by \( D_2 \) receptors
- Increased exploration & locomotion (thought to be connected to dopaminergic activity in the nucleus accumbens).
- Sexual behavior in the male is increased by dopamine agonists, whereas sexual behavior in the female is increased by dopamine antagonists.
NOREPINEPHRINE (NORADRENALINE)

Synthesis:
Dopamine----- Dopamine Beta-Hydroxylase enzyme ----> Norepinephrine

I. The most prominent noradrenergic nucleus is the locus ceruleus in the pons

II. Electrical stimulation of the locus ceruleus produces a state of arousal and wakefulness. The noradrenergic system seems to be important for attention.
SEROTONIN
(5-HYDROXYTRYPTAMINE, 5-HT)

I. Serotonin is primarily used for synthesis of melatonin.

II. Melatonin is of particular importance for regulating diurnal (circadian) & seasonal behavior & physiology in mammal. It is highly secreted at night (low secretion during the day)

III. Serotonin and norepinephrine transmitters are effective against depression.
PEPTIDES

I. Peptides are the most common neurotransmitters in the hypothalamus.

II. They are all synthesized on ribosomes and are all inactivated by hydrolysis at the synapse (rather than by reuptake).

III. Peptides are far more potent than other neurotransmitters, requiring only very small amounts to produce a profound effect.
I. **Opioid peptides** include the endorphins, enkephalins and dynorphins. They are associated with pain relief and pleasure.

II. Cholecystokinin (CCK) seems to function in the production of satiety.

III. Low doses of the peptide vasopressin have been shown to enhance learning in laboratory animals.