The important names

- **MONOAMINES:**
  - Acetylcholine
  - Serotonin
- **CATECHOLAMINES:**
  - Dopamine
  - Noradrenaline
  - Adrenaline
- **AMINO ACIDS:**
  - Glutamate
  - GABA (gamma-aminobutyric acid)
  - Glycine
- **Neuropeptides:**
  - Co-localised with the neurotransmitters; i.e. they coexist in the same synapses
- **Neuromodulators:** released into synapses to modify synaptic transmission
  - Adenosine, adenosine triphosphate, nitric oxide

**Receptors**

- Every ligand has many subtypes of receptors
- Neurotransmitters have presynaptic as well as postsynaptic elements
- Presynaptic “autoreceptors” typically INHIBIT FURTHER RELEASE of the neurotransmitter
  - for example, noradrenaline acts on its own alpha-2 receptors to inhibit itself
  - receptors tend to cluster near the nerve endings that release their neurotransmitter
- Prolonged exposure to ligands tends to make receptors less responsive, i.e. undergo desensitization
  - HOMOLOGOUS desensitization is when the cell is ONLY desensitized to that one neurotransmitter
  - HETEROLOGOUS desensitization causes the cell to become less responsive to all other ligands

**Reuptake**

- Neurotransmitters are recycled out of the synapse by reuptake mechanisms, getting sucked back into the cytoplasm of the neuron which secreted them
- There are two families of transporters:
  - One co-transport noradrenaline, dopamine, GABA, glycine etc- co-transport with Na⁺ and Cl⁻
  - The other family transports only glutamate, and is coupled to co-transport of Na⁺ and countertransport of K⁺
- Inside the cell, there are two vesicular monoamine transporters: VMAT1 and VMAT2
- They transfer the reabsorbed neurotransmitter back into the vesicles
- They have little specificity- they will just take anything and drag it back into the vesicles
- They are inhibited by RESERPINE: an old-school antihypertensive and antipsychotic
- Reuptake is the main way of getting neurotransmitters to stop working
- Inhibition of reuptake causes increased neurotransmitter effects
**Excitotoxicity**

- GLUTAMATE is unique: it can produce so much Ca\(^{++}\) influx that neurons die.
- It is removed from the synapse by a Na\(^+\)-mediated transport
- Thus, if you can't maintain an Na\(^+\) gradient, you can't pump glutamate
- If you can't pump glutamate, you die.
- This is something that happens at the borders of a stroke (the “penumbra”), where cells are partially ischaemic and haven't died, but can no longer maintain their Na\(^+\) gradient

**Small Molecule Neurotransmitters**

**ACETYLCHOLINE**

- An ester of choline
- Synthesized from choline and acetate by choline acetyltransferase; cholinergic neurons actively suck choline up through a transporter.
- Taken up by a vesicular transporter VACHT into small, clear synaptic vesicles
- All preganglionic autonomic synapses, and all parasympathetic postganglionic synapses
- Involved in the regulation of the sleep-wake cycle, learning and memory
- “true” acetylcholinesterase is only found in the synapses; it breaks acetylcholine down so the postsynaptic cell can repolarise.
- There also “pseudocholinesterases” in the bloodstream

**ACETYLCHOLINE RECEPTORS**

- Come in nicotinic and muscarinic flavours
- Muscarinic receptors are found in parasympathetic postganglionic fibers and are blocked by atropine
- Nicotinic receptors are found in preganglionic autonomic synapses, and in muscle
- Both nicotinic and muscarinic receptors are abundant in the brain
- All of them are ligand-gated ion channels
- NICOTINIC receptors, when activated, allow cations of all sorts to cross the membrane
- This means, sodium comes in and potassium comes out
- MUSCARINIC receptors are all coupled to either G-proteins (and thus adenyl cyclase), potassium channels and phospholipase C.

**SEROTONIN**

- 5-hydroxytryptamine
- Found in great abundance in platelets and in the gastrointestinal tract
- Formed by hydroxylation and decarboxylation of tryptophan
- After reuptake, it is captured and metabolised by Monoamine Oxidase into 5-HIAA- 5-hydroxyindoleacetic acid
- Considerable role in mood and behaviour:
  - LSD is a serotonin receptor agonist – acts on 5-HT2 receptors
  - In fact all hallucinogens seem to bind to these receptors
  - MDMA causes serotonin release
- There are swarms of receptors, and most types are G-protein-coupled. 5-HT3 are ion channels.

**HISTAMINE**

- Histaminergic neurons are found in the tuberomamillary nucleus of the posterior hypothalamus
- They project to almost everywhere in the brain
- It's also all over the gut and is an inflammatory mediator, but that's beside the point
- Formed by the decarboxylation of the amino acid histidine
- 3 types of receptors: H1, H2 and H3
- H1 receptors activate phospholipase C
- H2 receptors intracellular cAMP concentration
- Most of the H3 receptors are presynaptic and G-protein-coupled – inhibit the release of histamine and other neurotransmitters
Adrenaline, noradrenaline and dopamine
- Contained in dense-core granulated vesicles
- Formed by the hydroxylation and decarboxylation of tyrosine

NORADRENALINE and all the catecholamines is produced thus:

GLUTAMATE
- Main excitatory neurotransmitter
- 75% of the excitatory activity is glutamate-related
- Made from alpha-ketoglutarate (the Krebs cycle intermediate) by reductive amination
- Then, concentrated in vesicles by the glutamate-binding protein BPN1
- You can also get hold of extra glutamate from the extracellular fluid where it is floating (i.e. by reuptake)
- Some glutamate is reabsorbed into astrocytes, turned into glutamine, and then passed back to the neuron
- Uptake back into neurons and astrocytes is the main way of getting rid of synaptic glutamate, and this is a Na+ dependent process

GLUTAMATE RECEPTORS
- Two distinct flavours: METABOTROPIC and IONOTROPIC.
  METABOTROPIC:
  - G-protein coupled
  - Increase intracellular IP3 and DAG, or decrease cAMP
  - 11 varieties; they can be post or presynaptic
  - Seem to be involved in synaptic plasticity and learning

IONOTROPIC GLUTAMATE RECEPTORS: 3 types
- Ligand gated ion channels
  KAINATE receptors
  - When open, allow sodium influx and potassium efflux.
  - Located presynaptically on GABA nerve endings, and post-synaptically elsewhere
  - Kainate is a weird amino acid isolated from seaweed
  AMPA receptors
  - Two types: one is only for Na+, the other also allows Ca++
  NMDA receptors
  - Also a cation channel; Na+, K+ and Ca++
  - Requires glycine to bind to it in order to function
  - ONLY opens if the membrane is already partially depolarized- otherwise, a magnesium ion blocks it
  - Usually occurs together with AMPA receptors
GABA
- Main inhibitory neurotransmitter
- Formed by the decarboxylation of glutamate, by the aptly-named glutamate decarboxylase
- Catabolised into succinate (and plugged into the citric acid cycle) by GABA Transaminase

GABA RECEPTORS: 3 types, and they all hyperpolarize neurons
- **GABA-A**
  - Ligand-gated chloride channels
  - The targets of BENZODIAZEPINES
- **GABA-B**
  - Metabotropic- coupled to G-proteins; the effect is to increase potassium channel conductance and to decrease Ca** influx
- **GABA-C**
  - Ligand-gated chloride channels
  - Found exclusively in the retina in adult vertebrates

Glycine
- Both excitatory and inhibitory effects in the CNS
- Has a job sensitizing NMDA receptors
- Seems to spill out of the synapse into the extracellular fluid
- Like GABA it increases chloride conductance of membranes
- **ANTAGONISED BY STRYCHNINE- this causes a post-synaptic disinhibition, and thus convulsions**

Neuropeptides

**Substance P and the Tachykinins**
- Mediator of the first synapse in the dorsal horn of the spinal cord; involved in pain transmission
- Receptors are G-protein-coupled
- Activation of its receptor leads to activation of phospolipase C, as well as IP$_3$ and DAG

**Opioid peptides**
- The endogenous peptides are the ENKEPHALINS and ENDORPHINS
- 3 main forms of receptors: mu, kappa and delta
  - **Mu**: analgesia, respiratory depression, constipation, euphoria, miosis,
    - Increase K$^+$ conductance; bind only endorphins
  - **Kappa**: analgesia, diuresis, sedation, miosis
    - Closes Ca** channels
  - **Delta**: analgesia
    - Closes Ca** channels
- All three are G-protein coupled receptors which inhibit adenylyl cyclase

Other polypeptides and random substances
- SOMATOSTATIN
- VASOPRESSIN
- OXYTOCIN
- ADENOSINE – receptors blocked by caffeine
- CANNABINOIDs
- NITROUS OXIDE
- PROSTAGLANDINS
- Sex hormones and corticosteroids penetrate the brain easily