The Synapse

- The Synapse = **Presynaptic** cell releases NT into “**Synaptic Cleft**” (gap between cells), affects **Postsynaptic** cell
  - Cleft is typically 20–50 nm wide (nm =nanometer = 10^{-9} meter = one billionth of a meter)
- **Exocytosis** = The release of **Vesicles** (packets) of NT from Presynaptic Terminal
  - When membrane depolarization reaches the axon’s Terminal, voltage-dependent Ca^{++} gates open, extracellular Ca^{++} rushes into Terminal (per Electrical & Conc Gradients), causing release of NTs
  - NT passively flows (diffuses) across Synaptic Cleft
- **NT binds to NT-specific Receptor Site** on (usually) **Dendrites** of Postsynaptic cell
  - Binding to Receptor Site triggers reaction in Postsynaptic cell, which may lead to it firing its NT, etc
  - NT soon **detaches** from Receptor Site & again floats in Cleft (Most NTs do NOT enter Postsynaptic Cell)
  - NT is often then **deactivated** by enzymes or Glia in the cleft
    - i.e. NT broken down, carried off, re-uptaken by Presynaptic cell, etc
  - This prevents NT from continuing to affect Postsynaptic cell after message has been “sent”

NT can have two basic types of effects on the **polarity** of the Postsynaptic cell:

**EPSP** = **Excitatory Post-Synaptic Potential** = An increase that cell’s likelihood of releasing NT
  - i.e. Post-Syn cell becomes **Hypo-Polarized** (less polarized, less difference between inside and out)
  - and thus closer to its threshold for firing.
  - Usually a function of Na^{+} entering cell

**IPSP** = **Inhibitory Post-Synaptic Potential** = A decrease in the cell’s likelihood of releasing NT
  - i.e. Post-Syn cell becomes **Hyper-Polarized** (more polarized, greater difference between inside and out)
  - and thus farther from its firing threshold
  - Usually a function of K^{+} exiting or Cl^{-} entering the cell

**Summation** The response of a given Neuron is nearly always the product of a **Summation of EPSPs and/or IPSPs**
- A Neuron virtually never receives input from only one other cell, and can receive from 1000s of others!
- Often both excitatory and inhibitory NTs simultaneously converge on a cell, summatign their +/- effects
  - If **effects reach or exceed** cell’s **Threshold of Firing**, trigger an **Action Potential** (In cells that have AP’s)
  - When one (or more) cells repeatedly stimulate another in rapid succession, it is called **Temporal Summation**
  - When multiple cells converge on a single cell at the same time, the effect is called **Spatial Summation**

**Mechanisms** - NT affects the Postsynaptic cells via one of two types of mechanisms:
- **Ionotropic** = **Directly effects ion gates** e.g. NT binds to receptor site >> opens ion gate
  - Effects are rapid, short-lived, especially good for conveying info about rapidly changing event
- **Metabotropic** = Triggers **metabolic changes** in Postsynaptic cell e.g. NT alters receptor, releases G-Protein >> Activates/triggers production of **Second Messenger**, which binds w/G-Protein to open separate ion gate
  - Complex chain reaction requires energy - Effects are slower, longer lasting (up to hours!)

**Spontaneous Activity** – Important to note: Some Neurons show Spontaneous Firing, in absence of incoming NT!
- These are usually Graded Potentials that release variable amounts of NT
- Converging NTs increase or decrease such cells’ activity, modifying how much NT they will then release

**Neurotransmitters**:

- Technically, these chemicals are called “**Neurotransmitters**” if impact nearby neurons, “**Neuromodulators**” if they diffuse over long distances, affecting many cells, not necessarily triggering firing but altering likelihood, and the same chemicals are called “**Hormones**” when found circulating in bloodstream.
- **Acetylcholine (ACh)** - Important NT in PNS (e.g. > muscle movement); Also thruout brain for arousal…
- **GABA** - Most abundant inhibitory NT (Opens Cl- gates); Suppresses cortical activity, regulates anxiety…
- **Glutamate** – Most abundant excitatory NT (Opens Na+ gates); Roles in perception, memory, schizophrenia…
- **Serotonin (5-HT)** - Many different kinds, involved especially in sleep, mood regulation…
- The Catecholamines: **Dopamine (DA)**, **Noradrenaline (NE)** & **Epinephrine** (Adrenaline), Adrenaline, - Involved in arousal, depression, reinforcement, motor control…
  - Often act as Neuromodulators
- **Substance P** - A peptide (complex protein) released from pain receptors
- **Endorphins** - A peptide w/opiate effects - i.e. pain suppression, reinforcement; produced in “runner’s high”
  - “Endorphin” = “Endogenous Morphine”
- **Hormones** - e.g. Testosterone, Estrogen, Oxytocin, Insulin, CCK, Cortisol, Adrenalin (Epinephrine) etc.
  - Released by brain cells or glands, act as NTs, NMs or circulate in blood, affect Neurons, Muscles, Organs

**NOTE:** Same NT can have very different physiological and behavioral effects in different parts of the brain/body!

**Modifying the Message**

- Besides summation, info transmitted by Neurons can be modified in various ways
  - That is, variations in any of the above-described functions can affect the message sent. For example . . .

**Agonism and Antagonism**

- **Agonist** = chemical that increases effect of a NT
- **Antagonist** = chemical that decreases effect of a NT
  - e.g. ACh broken down in cleft by enzyme Acetylcholinesterase (AChE) into Choline (reuptaken) & Acetate
    - In patients with ACh deficit, can block enzyme so little available ACh repeatedly stimulates Postsyn cell
      - So, such an AChE-blocker is an ACh-Agonist
    - In contrast, a Choline Reuptake-blocker would prevent re-synthesis of ACh and so is a ACh-Antagonist
  - e.g. Serotonin (5-HT) typically remains intact, reuptaken whole into Presynaptic cell by Transporter Proteins
    - 5-HT-Agonist drugs like Prozac block reuptake of Serotonin, prolonging its effects on Postsynaptic Cell
    - 5-HT Antagonist like enzyme MAO converts Serotonin into inactive form that won’t affect Postsyn Cell
  - Antagonists and Agonists can also operate inside the Presynaptic cell to affect NT release
    - Some antagonistic drugs (e.g. Reserpine) prevent NTs (Monoamines) from being packaged into vesicles
    - Some agonists (like Black Widow Spider venom) cause massive release of NT (ACh)

**Other Factors that modify Function**

- Activation of DNA sequences initiated the production of proteins for structural and chemical changes within cell
- Receptor Sites can increase/decrease in number
  - e.g. Repeated activity ⇒ more Dendritic Spines, more receptor sites
- Receptor Sites can be blocked by NT mimics that do not readily detach
  - e.g. LSD binds to Serotonin sites
- Some NTs, like Substance P (Pain), are produced in Neuron’s soma, may require hours/days to replenish
  - Carried by Kinesin molecules (proteins) that “walk” along micro-tubules from soma to terminal
  - Others, like Acetylcholine (ACh) , are produced in Terminal & are efficiently recycled from cleft
  - Can depend on diet for availability of precursors
    - e.g. Tryptophan in turkey >> Serotonin
    - e.g. Choline from milk or synthesized from lecithin >> ACh
  - A few precursors (like L-DOPA for Dopamine) will pass blood-brain barrier, so can be administered as drugs

**EXCEPTIONS: Receptor Sites on PRE-synaptic Terminal**

- **Auto-Receptors** - Some Axons have Receptor Sites for their own (usually inhibitory) NT
  - NT binding with these sites ⇒ Negative Feedback Loop via Second Messengers within PRESynaptic cell
    - That is, their own NT prevents them from releasing more NT
  - e.g. By closing own Ca++ gates -or- blocking reset of Resting Potential by interfering with Na+/K+ Pump
- **Axoaxonic** Synapses (Axon to Axon)
  - Presynaptic Terminal may have Receptor Sites for Inhibitory or Excitatory NT from another cell
  - e.g. Brain Endorphins stimulate opiate receptors on terminal of pain cell, inhibiting release of Substance P