Cogs17 Neurobiology of Cognition

Lecture 2b: Structure & Function of Cells in the Nervous System * CONTINUED

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 Postynaptic 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, summating 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), Norepinephrine (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

NOTE: Either can result in excitation or inhibition, depending on type of NT

- **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 Acetylcholin**esterase** (**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 Prosac 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 **Dendridic 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 **PRE**synaptic 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)
  - –**Pre**synaptic 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