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Zak Fallows

SP.236: The Steps of Neural Signaling

Information:
The steps below represent the path taken by the information being communicated, the message, the signal itself.

Step 1: Afferent (incoming) action potential arrives
Location: Presynaptic terminal
Inhibited by: Ethanol, anticonvulsants, tetrodotoxin (TTX, from puffer fish)
Enhanced by: Metrazol, epileptic seizures, electroconvulsive therapy (ECT)

Step 2: Neurotransmitter-filled vesicles fuse with the cell membrane and empty their contents into the synaptic cleft (exocytosis)
Location: Presynaptic terminal
Inhibited by: Botulinum toxin (Botox®), tetanospasmin (from tetanus)
Enhanced by: Certain types of learning, frequent use (in some cases)

Negative feedback regulation: There are often inhibitory autoreceptors on the presynaptic terminal that sniff the level of neurotransmitter already present, and if the level is too high then the presynaptic neuron chooses not to release more neurotransmitter. This is negative feedback, just like a thermometer controlling a furnace (a thermostat). Examples:

Clonidine is an agonist of presynaptic inhibitory autoreceptors on adrenergic (NE releasing) terminals. Because it is an agonist, it is like holding a match under the thermostat, which turns off the furnace and makes the house cold. Clonidine reduces NE release, lowering blood pressure and inducing sleep.
Mirtazapine, mianserin, and **yohimbine** are antagonists at presynaptic inhibitory autoreceptors, they increase release of 5-HT and NE. This is analogous to holding ice on a thermostat, which makes the house very hot.

Step 3: Neurotransmitter diffuses from the presynaptic to the postsynaptic side of the synaptic cleft

Step 4: Neurotransmitter binds to receptors
Location: Postsynaptic terminal
Inhibited by: Antagonists, which fill up receptors and displace neurotransmitter
Enhanced by: Agonists, which mimic the neurotransmitter

Step 5: The appropriate signal is sent in the postsynaptic cell.

This signal may be inhibitory (decreases likelihood of an action potential), or excitatory (increases likelihood of an action potential), or modulatory (does something complex).

Branch A: An ion channel opens. Receptors which contain an ion channel are called *ionotropic*, and when the neurotransmitter binds and causes ions to flow, the postsynaptic cell is either depolarized or hyperpolarized, and this sends an excitatory or inhibitory signal, respectively.

Branch B: The receptor does not contain an ion channel, instead it is a G-protein coupled receptor (GPCR), also called a *metabotropic* receptor.

Step 5.B.1: The G-protein is activated
Step 5.B.2: An enzyme (or ion channel) is activated (or opened)
Step 5.B.3: This enzyme makes a second messenger molecule, such as cAMP, cGMP, IP3, or DAG
Step 5.B.4: The second messenger passes along the signal

Viagra® (sildenafil) works at this step. Viagra inhibits the breakdown of cGMP, so this second messenger builds up and its signal is enhanced.

Neurotransmitter:
The steps below represent the life cycle of a molecule of neurotransmitter, which is an actual physical substance, in contrast to the notional information that we followed above.

Step 1: Synthesis

Enhanced by:

Providing the precursor molecule

Tryptophan or 5-HTP → 5-HT

Levodopa → DA and NE

Getting the precursor into the brain

Sugar → Insulin → increased 5-HT synthesis

Inhibited by:

Inhibit synthesis enzyme

AMPT → inhibits enzyme → decreases NE and DA synthesis

Step 2: Package in vesicles

Inhibited by:

Reserpine

Amphetamine

(Note that reserpine and amphetamine have opposite effects in the long run, because reserpine causes the unpackaged neurotransmitter to be broken down, but amphetamine causes the unpackaged neurotransmitter to leak into the synapse)

Step 3: (*same as information Step 2*) Neurotransmitter-filled vesicles fuse with the cell membrane and empty their contents into the synaptic cleft (exocytosis)

Step 4: (*same as information Step 3*) Neurotransmitter diffuses from the presynaptic to the postsynaptic side of the synaptic cleft

Step 5: (*same as information Step 4*) Neurotransmitter binds to receptors

Step 6: (*optional*) Reuptake into presynaptic cell by proteins called *transporters*

- Inhibited by: Reuptake inhibitors
  - SSRIs (selective serotonin reuptake inhibitors)
  - TCAs (tricyclic antidepressants)
  - Amphetamine

Step 7: Breakdown (metabolism)

- Location:
  - Occurs in the synapse if there was no reuptake (e.g. ACh)
  - Occurs inside the presynaptic cell if there was reuptake
- Inhibited by:
  - MAOIs (monoamine oxidase inhibitors) → Boost 5-HT, NE, DA
  - Vigabatrin → Boosts GABA
- Enhanced by:
  - Reserpine → Causes breakdown of 5-HT, NE, DA

ES.S10 Drugs and the Brain

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