Physiology Lecture Outline: Neurotransmitters

Neurotransmitters (NT’s) are signal molecules that are released from neurons. There are believed to be about 60 known neurotransmitters. They can function as excitatory or inhibitory substances, but this can change depending on the location of neuron and type of effector (target) cell it acts on. For example, Acetylcholine (ACh) contracts skeletal muscle and ACh relaxes smooth muscle! How can the same NT have contrasting effects on various tissues? The answers lies in the type of receptor on the target tissue. The specific type of receptor on the tissue will determine how the tissue responds to various signal molecules.

Figure 1. Above is the “Simple Guide to Neurotransmitters” graphic giving an overview which is shared from the website www.compoundchem.com/2015/07/30/neurotransmitters

Excitatory Neurotransmitters: These types of neurotransmitters have excitatory effects on other neurons or the effector tissue it innervates. If acting on another neuron at a synapse it causes a depolarization of the postsynaptic membrane which can be termed an excitatory postsynaptic potential (EPSP) because it increases the likelihood that the effected neuron will fire an action potential. Some of the major excitatory neurotransmitters include epinephrine and norepinephrine.

Inhibitory Neurotransmitters: These types of neurotransmitters have inhibitory effects on other neurons or the effector tissue it innervates. If acting on another neuron at a synapse it causes a hyperpolarization of the postsynaptic membrane which can be termed an inhibitory postsynaptic potential (IPSP) because it decreases the likelihood that the effected neuron will fire an action potential. Some of the major inhibitory neurotransmitters include serotonin and gamma-aminobutyric acid (GABA).
Some neurotransmitters can be both excitatory and inhibitory effects. That is, they can cause EPSP’s or IPSP’s, but this depends on the location of neuron and type of receptors on the effector (target) cell it acts on. These include neurotransmitters such as acetylcholine and dopamine.

**Agonists** and **Antagonists**: Some substances are known as agonists because they function by increasing the effects of specific neurotransmitters, while other substances are referred to as antagonists because they act to block the effects of a neurotransmitter.

**Neurotransmitters can be divided into four categories**

1. Acetylcholine (ACh)
2. Amino Acids
3. Biogenic Amines
4. Neuropeptides

**ACh** - This is a single molecule that is in a class all by itself. It *ubiquitous* (found everywhere) and found all over the nervous system. It is released by some neurons in the central nervous system (CNS) and many neurons in the peripheral nervous system (PNS). Neurons that release ACh are termed "Cholinergic" neurons. This neurotransmitter is perhaps best known as the one released by somatic motor neurons in the neuromuscular junctions (NMJ) of skeletal muscle.

ACh binds to two types of receptors, *nicotinic* and *muscarinic*, therefore these are called ‘Cholinergic’ receptors. In general terms, nicotinic receptors are always excitatory, meaning that when stimulated they depolarize the membrane and cause an EPSP. Muscarinic receptors are generally inhibitory, in that when stimulated they usually cause an IPSP.

ACh plays a role in voluntary motor control, ‘automatic’ control, memory, regulation of attention, learning, sleeping. In the PNS, ACh is the sole NT used by the Somatic Nervous System (SNS). At the NMJ ACh binds to nicotinic receptors on skeletal muscle and causes excitation (contraction) of skeletal muscle. In the Autonomic Nervous System (ANS), it is release by all neurons at the ganglia and binds to nicotinic receptors on postgalionic neurons. It is also released by parasympathetic postgalionic neurons and binds with muscarinic receptors on effector tissue (cardiac muscle, smooth muscle and glands).

**Amino Acids** - These NT’s can be excitatory or inhibitory.

**Excitatory**

1) **Glutamate** - accounts for approximately 75% of all excitatory transmission in the brain, so it is *the most common excitatory NT in the brain*. It is released in the cerebral cortex and brain stem. It is involved in cognitive functions, such as learning and memory. It also regulates brain development and creation of nerve contacts. If present in high concentration in the brain, possibly when monosodium glutamate (MSG) is ingested in high quantities, glutamate can be toxic to neurons and can act as an ‘excitotoxin’ over-exciting other neurons. Also called glutamic acid.

2) **Aspartate** - similar to glutamate but found mostly in the spinal cord for excitation (aspartic acid).
Inhibitory

3) GABA - Gamma AminoButyric Acid (GABA) is the most common inhibitory NT in the brain. Released in thalamus, hypothalamus, cerebellum, occipital lobe and retina. Its role is to inhibit the firing of nerves in the CNS and as a consequence it acts to calm neural processing. Increased GABA levels improve mental focus and relaxation, whilst low levels can cause anxiety, and have also been linked with epilepsy. GABA also contributes to motor control and vision. Drugs to treat epilepsy often act by increasing levels of GABA in the brain.

4) Glycine - is the simplest amino acid and is a common inhibitory NT in the spinal cord. It is also released in the brain and retina.

3) **Biogenic Amines** - These NT's are all derived from either the amino acid tyrosine or tryptophan. The COOH groups in the amino acid are replaced by NH$_2$ groups. There are two main categories of Biogenic Amines, they are A) **Catecholamines** (derived from tyrosine) and B) **Indolamines** (derived from tryptophan). All of these can also be referred to as monoamines, which are degraded by the enzyme **MonoAmine Oxidase** (MAO).

A) **Catecholamines** - three main catecholamines: Epinephrine (E), Norepinephrine (NE) and Dopamine.

1) **Norepinephrine** (NE) - released by most sympathetic postganglionic nerve fibers. It is also released in the cerebral cortex, hypothalamus, brain stem, cerebellum and spinal cord. It has a role in mood, dreaming, wakefulness and alertness levels. This used to be called noradrenaline and that is why neurons that release NE or epinephrine (E) are termed "Adrenergic" neurons. Both NE and E bind to alpha ($\alpha$) and beta ($\beta$) receptors, which are called adrenergic receptors.

For the most part, NE is an excitatory or stimulatory NT, typically elevating mood and alertness. Both NE and E are also released by the adrenal gland, specifically the adrenal medulla, when it is stimulated by the Sympathetic division of the ANS. Most, predominantly E is released (80%) and to a much lesser degree NE (20%).

* The highly addictive drug **cocaine** interferes with NE transmission in the brain. Cocaine acts to block the reuptake of NE back into adrenergic neurons that released it. This has an effect of increasing the amount of NE that lingers in the synaptic cleft, thus increasing the stimulatory effects on the target cell.

* There are also drugs that inhibit the effects of the degradative enzyme Monoamine Oxidase (MAO), they are called **Monoamine Oxidase Inhibitors** (MAO Inhibitors). They have their effect by increasing the amount of NE that remains in the synaptic cleft, as well as increasing the amount of NE that is packaged into the vesicle before being released into the synaptic cleft. Some medications act to reduce the amount biogenic amine action in the body and are used for high blood pressure (e.g., reserpine) but can have the side effect of causing depression. This is because decreased (or depressed) levels of biogenic amines in neural transmission is linked to clinical depression.
2) **Epinephrine** (E) - released in thalamus, hypothalamus, spinal cord and adrenal medulla. Chemically and functionally very similar to the effects of NE. It is important for forming memories. The name epinephrine means above (epi), the kidneys (nephron) in relation to the location of the adrenal glands that sit on top of each kidney. It is E that is predominantly released from the adrenal gland. When released this way, it acts as a hormone. As a hormone it is released in highly stressful or exciting situations. It stimulates increased heart rate, contracts most blood vessels, and dilates airways, to divert blood flow to the muscles and oxygen to the lungs. This leads to a physical boost, and heightened awareness. Stress tends to deplete our store of adrenalin, while exercise tends to increase it. **EpiPens**, which are used to treat allergic reactions, work by injecting epinephrine directly into the body via intramuscular (IM) injection.

3) **Dopamine** – released by the cerebral cortex, hypothalamus, limbic system and retina. It is highly concentrated in the **substantia nigra** of the midbrain where it is involved with voluntary motor control. Also involved in elevation of mood and emotional responses. In the brain it is involved in reward, motivation and is associated with feelings of pleasure and satisfaction. It is also associated with addictive behavior. The feelings of satisfaction caused by dopamine can become highly desired, and to satisfy this a person will repeat behaviors that lead to release of dopamine, related to the ‘pleasure center’ in the brain. These behaviors can be balanced, or they can become unbalanced, such as detrimental drug addictions. It is also involved in memory and attention, e.g. the limbic system is involved in elevation of mood and emotional responses. Neurons that release dopamine are termed "**Dopaminergic**" neurons.

* Dopaminergic neurons in the subsancia nigra normally inhibit primary motor neurons (which then control skeletal muscle fibers). Degeneration of dopaminergic neurons in the subsancia nigra can lead to **Parkinson’s disease**. L-Dopa is a precursor to dopamine and used as a medication for Parkinson’s disease, as it can pass through the blood brain barrier, whereas dopamine cannot. It’s postulated that too much Dopamine activity is involved in schizophrenia.

* It has also been hypothesized that the consumption of chocolate increases dopamine transmission, and thus this is part of the reason why eating chocolate may lead to feeling good. Dopamine transmission has also been linked to reward centers in the brain (like the ‘pleasure’ center) and has been associated with addictive behavior.

* **Amphetamine** ("speed") is a drug that works by causing an augmented release of the neurotransmitters norepinephrine, dopamine and serotonin. This is thought to occur by stimulating a greater release of these neurotransmitters from the synaptic end bulb, as well as reducing the reuptake mechanisms, and inhibiting MOA degradation of these. All of these occurrences increase the effects of these neurotransmitters on the central nervous system.

**Upregulation and Downregulation – let’s mention this now!**
As for all of the drugs and other addictive substances discussed, a key element to the sensitivity of a target cell for any signal molecule is **receptor density**. Receptors on the plasma membrane of cells are there to receive signals and allow the cell to respond. In relation to our discussion of neurotransmitters, the more receptors a cell has for that specific molecule, the more strongly the cell will respond to it.
Receptors levels can be fine-tuned and changed. It can be increased (upregulated) if the signal is too faint or diminished, or it can be decreased (downregulated), if the signal is too strong or overwhelming.

**Upregulation** of receptors is when the cell increases receptor density in response to a stimulus. **Downregulation** of receptors is when a cell decreases receptor density in response to a stimulus.

This is a great example of negative feedback in the body. Downregulation of receptors occurs after chronic exposure to an excessive amount of a ligand (e.g. a hormone or neurotransmitter). The consequence is that the cell becomes ‘desensitized’ to that substance and will required a greater amount in order to evoke a similar response to the previous stimulus. This is the hallmark of ‘addiction’, as the practice continues ‘more’ stimulus is required for less and less response. On the contrary, the upregulation of receptors can ‘super-sensitize’ cells. This can be seen after a prolonged absence of the ligand; when it is re-introduced there is an elevated sensitivity to even small amounts of it. Note: The use of antagonistic drugs, by preventing true ligands from downregulating receptors, may have the effect of upregulating receptors when withdrawn.

**B) Indolamines** - two main indolamines: Serotonin (5-HT) and Histamine.

4) **Serotonin** (5-HT) - released in the hypothalamus, limbic system, cerebellum, retina and spinal cord. Serotonin is derived from the amino acid tryptophan. It is secreted by platelet cells where it is associated with wound healing. It is believed to play a role in sleepiness, alertness, mood and thermoregulation. In addition, serotonin is also found in abundance in your gut (digestion system). It is a natural mood stabilizer, it helps with sleeping, eating, and digesting, thus plays an important role in sleepiness, alertness, mood and thermoregulation.

*Serotonin is also affected by MAO Inhibitors. For example, the drugs phenelzine (Nardil) and isocarboxazide (Marplan) are also used to treat clinical depression. These also have an effect of increasing the amount of NE in the synaptic cleft, as well as increasing the amount of NE that is packages into the vesicle before being released into the synaptic cleft. This elevated NE response tends to be seen in the sympathetic division of the ANS, so “dry mouth”, elevated heart rate and increased blood pressure are significant side effects experienced by people on this type of medication.
* Often MonoAmine Oxidase is located inside the presynaptic neuron where it degrades NT that has been actively transported back into the cell that released them. In these cells, inhibition of MAO is believed to increase the amount of serotonin packaged into the vesicle before being released into the synaptic cleft. Again, this would increase the amount of serotonin released and increase serotonergic effects.

* Some medications prescribed for depression, such as fluoxetine (Prozac) and paroxetine (Paxil), interfere with serotonin transmission in the brain. They both prevent reuptake of serotonin by presynaptic neurons. This represented a new class of antidepressants called selective serotonin reuptake inhibitors (SSRIs). This results in an increased amount of serotonin remaining in the synaptic cleft, thus serotonin-dependent activity in the CNS increases. These effects are analogous with the effects of cocaine for NE neurons. The SSRIs are more specific than MAO inhibitors because they only target serotonergic synapses.

5) Histamine - released by the hypothalamus but little is known about its specific actions as a NT. Also released by mast cells and basophils. Acts as a paracrine and vasodilates blood vessels (causing local heat) and increased vascular permeability (causing local puffiness).

4) Neuropeptides - These NT's can be from 2 to 40 amino acids in length. There are many neuropeptide but we will limit our discussion to three: Substance P, Enkephalins and β-Endorphins.

1) Substance P - released by neurons of the basal nuclei, midbrain, cerebral cortex and hypothalamus. This is a very important NT for mediation of pain transmission and pain perception pathway. The P is for Pain. Sub P also causes vasodilation and is a trigger for nausea and vomiting.

2) Enkephalins - released in hypothalamus, limbic system, pituitary gland and pain pathways of the spinal cord. Also found in nerve endings of the G.I. tract. Enkephalins act as analgesics ('pain killers') by inhibiting substance P transmission. Levels of enkephalins increase significantly during child birth, being involved in blocking pain signals in the spinal cord.

3) β-Endorphins - found in many parts of the brain and the G.I. tract, also a hormone in the pituitary gland. β-Endorphins are opioid peptides (similar in chemical nature to opium) and are part of the body's natural pain relief molecules. This NT also suppresses pain by blocking substance P transmission and reduces the perception of fatigue. The release of endorphins can be triggered in multiple ways and it acts by reducing pain perception in the brain. These neurons engage in pre-synaptic inhibition of Substance P transmission.

* Endorphins are released after prolonged physical exertion or during 'stressed' states. It is linked to 'runner's high', the often euphoric feeling experienced by individuals after an endurance run. In addition, these feelings may be elicited from enduring physical or emotional challenges, pain, or stress.