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Lecture title: # Mechanisms of Transmitter Secretion and Removal at Postganglionic Endings

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Summary:

Mechanisms of Transmitter Secretion and Removal at Postganglionic Endings

Secretion of Acetylcholine and Norepinephrine by Postganglionic Nerve Endings:

A few of the postganglionic autonomic nerve endings, especially those of the parasympathetic nerves, are similar to but much smaller than those of the skeletal neuromuscular junction. However, many of the parasympathetic nerve fibers and almost all the sympathetic fibers merely touch the effector cells of the organs that they innervate as they pass by, or in some cases, they terminate in connective tissue located adjacent to the cells that are to be stimulated. Where these filaments touch or pass over or near the cells to be stimulated, they usually have bulbous enlargements called varicosities. It is in these varicosities that the transmitter vesicles of acetylcholine or norepinephrine are synthesized and stored. Also in the varicosities are large numbers of mitochondria that supply adenosine triphosphate, which is required to energize acetylcholine or norepinephrine synthesis. When an action potential spreads over the terminal fibers, the depolarization process increases the permeability of the fiber membrane to calcium ions, allowing these ions to diffuse into the nerve terminals or nerve varicosities. The calcium ions in turn cause the terminals or varicosities to empty their contents to the exterior. Thus, the transmitter substance is secreted.

Synthesis of Acetylcholine, Its Destruction After Secretion, and Its Duration of Action:

Acetylcholine is synthesized in the terminal endings and varicosities of the cholinergic nerve fibers, where it is stored in vesicles in highly concentrated form

until it is released. The basic chemical reaction of this synthesis is the following (CoA = coenzyme A):

$$\text{Acetyl-CoA + Choline} \xrightarrow{\text{Choline Acetylchacetyltransferase}} \text{Acetylcholine}$$

Once acetylcholine is secreted into a tissue by a cholinergic nerve ending, it persists in the tissue for a few seconds while it performs its nerve signal transmitter function. Then it is split into an *acetate ion* and *choline*, catalyzed by the enzyme *acetylcholinesterase*, which is bound with collagen and glycosaminoglycans in the local connective tissue. This mechanism is the same as that for acetylcholine signal transmission and subsequent acetylcholine destruction that occurs at the neuromuscular junctions of skeletal nerve fibers. The choline that is formed is then transported back into the terminal nerve ending, where it is used again and again for synthesis of new acetylcholine**.**

Synthesis of Norepinephrine, Its Removal, and Its Duration of Action.

Synthesis of norepinephrine begins in the axoplasm of the terminal nerve endings of adrenergic nerve fibers but is completed inside the secretory vesicles. The basic steps are the following**:**

1. Tyrosine $\xrightarrow{\text{Hydroxylation}}$ Dopa
2. Dopa $\xrightarrow{\text{Decarboxylation}}$ Dopamine
3. Transport of dopamine into the vesicles
4. Dopamine $\xrightarrow{\text{Hydroxylation}}$ Norepinephrine

In the adrenal medulla, this reaction goes still one step further to transform about 80% of the norepinephrine into epinephrine, as follows:

5. Norepinephrine $\xrightarrow{\text{Methylation}}$ Epinephrine

After secretion of norepinephrine by the terminal nerve endings, it is removed from the secretory site in three ways:

1- reuptake into the adrenergic nerve endings by an active transport process, accounting for removal of 50% to 80% of the secreted norepinephrine.

2- diffusion away from the nerve endings into the surrounding body fluids and then into the blood, accounting for removal of most of the remaining norepinephrine.

3- destruction of small amounts by tissue enzymes. One of these enzymes is monoamine oxidase, which is found in the nerve endings, and another is catechol-O-methyl transferase, which is present diffusely in the tissues. Ordinarily, the norepinephrine secreted directly into a tissue remains active for only a few seconds, demonstrating that its reuptake and diffusion away from the tissue are rapid. However, the norepinephrine and epinephrine secreted into the blood by the adrenal medullae remain active until they diffuse into some tissue, where they can be destroyed by catechol-O-methyl transferase; this action occurs mainly in the liver. Therefore, when secreted into the blood, both norepinephrine and epinephrine remain active for 10 to 30 seconds, but their activity declines to extinction over 1 minute to several minutes.

Receptors On The Effector Organs

Before acetylcholine, norepinephrine, or epinephrine secreted at an autonomic nerve ending can stimulate an effector organ, it must first bind with specific receptors on the effector cells. The receptor is on the outside of the cell membrane, bound as a prosthetic group to a protein molecule that penetrates all the way through the cell membrane. Binding of the transmitter substance with the receptor causes a conformational change in the structure of the protein molecule. In turn, the altered protein molecule excites or inhibits the cell, most often by:

1- Causing a change in cell membrane permeability to one or more ions.

2- Activating or inactivating an enzyme attached to the other end of the receptor protein, where it protrudes into the interior of the cell.

Neurotransmitters Other Than Acetylcholine and Norepinephrine Play Some Role in Peripheral Autonomic Function

*As more of a rule than an exception, individual neurons are capable of releasing more than one neurotransmitter.

*Multiple release often depends upon how vigorously the neurons are activated by presynaptic stimulation. Therefore, preganglionic and postganglionic sympathetic and parasympathetic neurons that release either acetylcholine or norepinephrine are respectively capable of releasing co-transmitters under certain circumstances.

*Most often these co-transmitters are peptides (e.g., vasoactive intestinal peptide, neuropeptide Y, luteinizing hormone-releasing hormone), but some purine (e.g., ATP) and atypical neurotransmitter (e.g., nitric oxide) co-release has been demonstrated as well. Often the postsynaptic response to release of a neurotransmitter is modified by the release of a co-transmitter from the same neuron. For example, acetylcholine released from parasympathetic postganglionic neurons can activate salivary glands, but co-release of vasoactive intestinal peptide from the same neurons can affect blood vessel diameter in the target region as well.

*Acetylcholine and norepinephrine can also be found in the enteric nervous system: acetylcholine is released by excitatory enteric neurons of the gut, and postganglionic sympathetic neurons can release norepinephrine into enteric neuronal plexuses to induce inhibition. Like the sympathetic/parasympathetic systems, various enteric neurons also employ vasoactive intestinal peptide, neuropeptide Y, ATP, and nitric

oxide. However, the variety of neurotransmitters other than acetylcholine and norepinephrine, employed by neurons of the enteric nervous system, is much more extensive than that found among the sympathetic and parasympathetic systems.