Pharmacology 659

Introduction to the Autonomic Nervous System

Charles B. Smith, M.D., Ph.D.
Fall Term, 2010

317A MSRB III
7343-763-9825
cbsmith@umich.edu
Autonomic Nervous System

The autonomic nervous system is that portion of the nervous system which maintains homeostasis within the internal environment of the body. It is also called the visceral, vegetative, or involuntary nervous system.

Claude Bernard (1813-1878)
The autonomic nervous system was divided by Langley into three parts: sympathetic, parasympathetic, and enteric (intestinal) systems.

Professor John Newport Langley, an outstanding English physiologist and histologist, member of the London Royal Society and its Vice-President. The main scientific achievements of Langley are dealing with anatomy and physiology of the autonomic (vegetative) nervous system that he considered as an entirely efferent system, and establishing functional differences of the autonomic nervous system from the somatic one. He suggested the presence of synaptic contacts on muscle and secretory cells, as well as the existence in these synaptic structures of a peculiar receptor substance providing interaction of nerve fibers with postganglionic neurons and effector cells of visceral organs.
### Differences Between Autonomic and Somatic Nerves

<table>
<thead>
<tr>
<th>Autonomic</th>
<th>Somatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervate heart, blood vessels,</td>
<td>Innervate skeletal muscle</td>
</tr>
<tr>
<td>glands, viscera, smooth muscle</td>
<td></td>
</tr>
<tr>
<td>Most distal synapses are in</td>
<td>Penultimate synapses lie</td>
</tr>
<tr>
<td>ganglia outside of the CNS</td>
<td>within the CNS</td>
</tr>
</tbody>
</table>

Lecture 6
Differences Between Autonomic and Somatic Nerves

Autonomic
- Postganglionic nerves are generally nonmyelinated
- Denervated effector organs show activity independent of intact innervation.

Somatic
- Motor nerves to skeletal muscle are myelinated
- Denervated skeletal muscles are completely paralyzed and undergo atrophy.

Lecture 6
“Flight and Fright Theory”

Cannon’s early research on gastrointestinal motility led to pioneering research on the physiological basis of the emotions and to the development of the concept of the emergency function of the sympathetic nervous system.

Walter Bradford Cannon
(1871-1945)
# Differences Between Sympathetic and Parasympathetic Nerves

<table>
<thead>
<tr>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution widespread</td>
<td>Distribution discrete and limited.</td>
</tr>
<tr>
<td>A single preganglionic fiber can synapse with many postganglionic fibers</td>
<td>A single preganglionic fiber synapses with only one postganglionic fiber.</td>
</tr>
<tr>
<td>Ganglia are frequently far removed from innervated organ</td>
<td>Ganglia are usually in or near the organ that is innervated.</td>
</tr>
</tbody>
</table>

Lecture 6
Motor fiber

Skeletal muscle

Somatic

Sympathetic

Ganglion

Pre-ganglionic fiber

Post-ganglionic fiber

Somatic

Sympathetic

Ganglion

Pre-ganglionic fiber

Post-ganglionic fiber

ACh

Smooth muscle

Cardiac muscle

Gland cells

Lecture 6
Sweat glands

Sympathetic

Adrenal medulla

Parasympathetic

Epinephrine
Norepinephrine

Smooth muscle
Cardiac Muscle
Gland Cells

ACh

ACh

ACh
Transmitters, Modulators and Hormones

Nerve Terminal

Synaptic cleft

Modulator

Transmitter

Lecture 6

Hormone
Factors Relevant to the Pharmacology of Neurotransmission at Autonomic Synapses

- Transmitter Synthesis
- Transmitter Storage
- Transmitter Release
- Receptor Activation
- Transmitter Inactivation

Lecture 6
Monoaminergic Synapse

Lecture 6
Neurotransmitter Synthesis

Lecture 6
Norepinephrine Synthesis

Tyrosine

\[
\begin{align*}
\text{Tyrosine} & \quad \text{Tyrosine Hydroxylase} \\
\text{DOPA} & \quad \text{DOPA Decarboxylase} \\
\text{Dopamine} & \quad \text{Dopamine \( \beta \)-Oxidase} \\
\text{Norepinephrine} & 
\end{align*}
\]

Lecture 6
Neurotransmitter Synthesis
Rate-limiting Steps

- Norepinephrine, epinephrine and dopamine
  Tyrosine Hydroxylase
- Serotonin
  Tryptophan Hydroxylase
- Acetylcholine
  Choline Uptake
- Feedback Regulation
  End Product Inhibition

Lecture 6
Neurotransmitter Storage

Lecture 6
Storage

Norepinephrine

Serotonin

Acetylcholine

ATP   CA

Chromogranin

Lecture 6
Neurotransmitter Release

Lecture 6
Neurotransmitter Release
(Exocytosis requiring Ca\(^{++}\) and Mg\(^{++}\))

I  II  III  IV

Norepi
ATP
CG\(_{A}\)

Lecture 6
Vesicle targeting, attachment and fusion

From Bajjalieh, 1999

Lecture 6
Additional Regulators that Increase the Precision of Exocytosis at the Synapse

- **Synapsin.** A unique actin-binding protein found in neurons that links synaptic vesicles to the cytoskeleton in a phosphorylation-dependent manner.

- **Synaptotagmins.** A family of calcium-binding proteins that can either brake or accelerate exocytosis at the synapse.

- **CAPS (calcium-dependant activator proteins).** Potential regulators of synaptic vesicle fusion required to reconstitute calcium-dependent catecholamine secretion in permeabalized neuroendocrine cells. It is possible that CAPS-like proteins constitute a family of factors specific to different types of calcium-regulated secretion, perhaps underlying differences in speed and plasticity.
Receptor Activation

Lecture 6
The Agonist-Receptor-Transducer Protein Complex

Agonist

+ → Complex + Transducer → Agonist-Receptor Transducer-Complex → Pharmacological Effect

Lecture 6
Events between binding of a drug to a specific receptor and effect
G Protein-Coupled Receptor Systems

G protein-coupled receptors

\[ \text{GTP} \quad \text{Lecture 6} \quad \text{GDP} \]

Effector
Regulatory Cycles Involved in G Protein-Mediated Signal Transduction

P_i
GTPase activity of α subunit

Lecture 6
Neurotransmitter Inactivation

Lecture 6
Diffusion

MAO

NE

5-HT

Metabolites

Lecture 6
Uptake

Lecture 6
Metabolism

MAO

DOMA
DOPEG
5-HIAA

NE
5-HT

NE → NMN
COMT

Lecture 6
Oxidative Deamination of Norepinephrine

Norepinephrine → 3,4-Dihydroxyphenyl-glycolaldehyde

Norepinephrine

3,4-Dihydroxyphenyl-glycolaldehyde

Aldehyde Reductase

DOPEG

DOMA

Lecture 6
Norepinephrine Metabolism

- Norepinephrine
- Normetanephrine
- DHPGAL
- DOPEG
- MOPEG
- HMA
- DOMA
- VMA
- MHPGAL
- MOPEG

Enzymes involved:
- MAO
- COMT
- Aldehyde dehydrogenase

Lecture 6
Noradrenergic Synapse

Tyr → DOPA → DA → NE

NE → NMN

COMT

MAO

DOMA

DOPEG

NE

Lecture 6